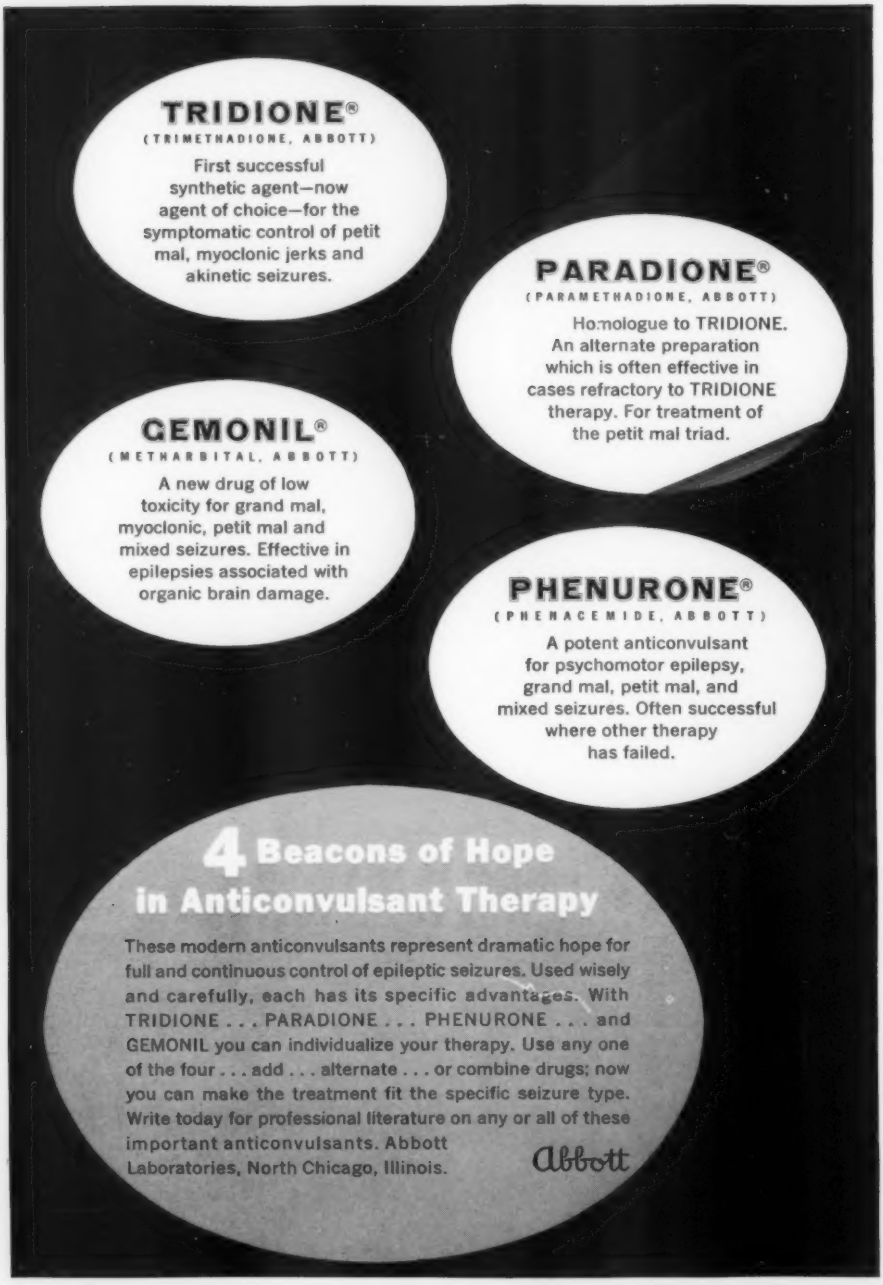
Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

JULY — 1955

Volume 5 — Number 7


TRIDIONE®
(TRIMETHADIONE, ABBOTT)
First successful synthetic agent—now agent of choice—for the symptomatic control of petit mal, myoclonic jerks and akinetic seizures.
PARADIONE®
(PARAMETHADIONE, ABBOTT)
Homologue to TRIDIONE. An alternate preparation which is often effective in cases refractory to TRIDIONE therapy. For treatment of the petit mal triad.
GEMONIL®
(METHARBITAL, ABBOTT)
A new drug of low toxicity for grand mal, myoclonic, petit mal and mixed seizures. Effective in epilepsies associated with organic brain damage.
PHENURONE®
(PHENACEMIDE, ABBOTT)
A potent anticonvulsant for psychomotor epilepsy, grand mal, petit mal, and mixed seizures. Often successful where other therapy has failed.
4 Beacons of Hope in Anticonvulsant Therapy
These modern anticonvulsants represent dramatic hope for full and continuous control of epileptic seizures. Used wisely and carefully, each has its specific advantages. With TRIDIONE . . . PARADIONE . . . PHENURONE . . . and GEMONIL you can individualize your therapy. Use any one of the four . . . add . . . alternate . . . or combine drugs; now you can make the treatment fit the specific seizure type. Write today for professional literature on any or all of these important anticonvulsants. Abbott Laboratories, North Chicago, Illinois.
Abbott

A NEW EMOTIONAL STABILIZER FOR NEUROPSYCHIATRIC THERAPY

Serpasil, in a recent study,[1] proved to be a valuable supplement in the treatment of neuropsychiatric conditions, including schizophrenia, paranoid and manic states, general paresis with psychosis and some cases of depression. In many instances it eliminated the need for electroshock therapy, restraints, seclusion and barbiturate sedation.

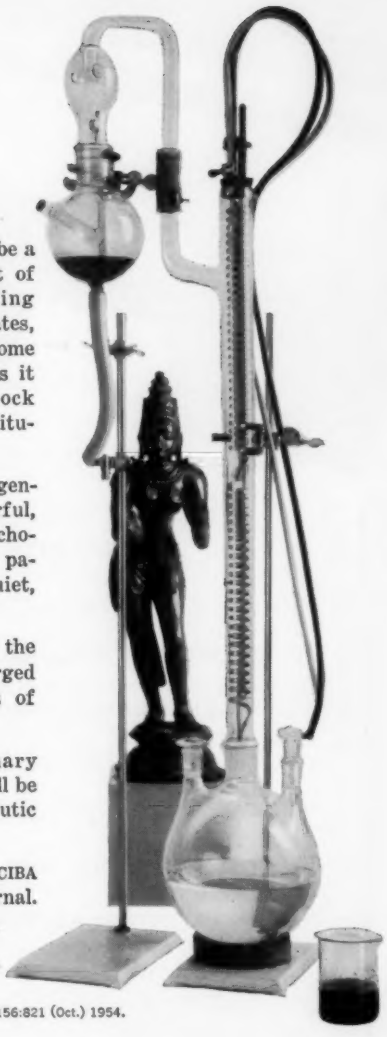
Combative, uncooperative patients in general became friendly, cooperative, cheerful, sociable and more amenable to psychotherapy under Serpasil. Hyperactive patients became sedate, noisy patients quiet, depressed patients alert.

Serpasil produced remissions in 20 of the 74 patients studied. Eight were discharged from the hospital. Long-term effects of treatment have not been determined.

If extended studies confirm preliminary findings, the authors state, Serpasil will be one of the most important therapeutic agents in the history of psychiatry.

Dosage information will be found in a CIBA advertisement elsewhere in this journal.

Parenteral Solution (for psychiatric use only), 2.5 mg. Serpasil per ml., 2-ml. ampuls.
Tablets, 1.0 mg. (scored), 0.25 mg. (scored), 0.1 mg.
Elixir, 0.2 mg. Serpasil per 4-ml. teaspoonful.



1. Noce, R. H., Williams, D. B., and Rapaport, W.: J. A. M. A.: 156:821 (Oct.) 1954.

Serpasil®
(reserpine CIBA)

CIBA
SUMMIT, N. J.

SPECIFY

GRASS

MODEL

III

SERIES

ELECTROENCEPHALOGRAPHS

- LIFETIME ACCURACY
- DEPENDABLE PERFORMANCE
- ECONOMICAL TO BUY AND MAINTAIN
- CONVENIENT TO OPERATE AND SERVICE
- EXPANDABLE AND VERSATILE
- THE INTERNATIONAL STANDARD OF COMPARISON

GRASS INSTRUMENT COMPANY

101 OLD COLONY AVENUE - QUINCY, MASS.

INSTRUMENT MAKERS TO THE MEDICAL PROFESSION SINCE 1935

Volume 5 **Neurology** *Number 7*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

WALTER O. KLINGMAN, M.D., *President*
FRANCIS M. FORSTER, M.D., *President-Elect*
AUGUSTUS S. ROSE, M.D., *Vice-President*
THOMAS W. FARMER, M.D., *Secretary*
JOSEPH L. WHELAN, M.D., *Treasurer*

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*
Associate Editor: MABEL G. MASTEN, M.D., *Miami, Florida*
Editorial Board: PEARCE BAILEY, M.D., *Washington, D. C.*
FRANCIS M. FORSTER, M.D., *Washington, D. C.*
ROLAND P. MACKAY, M.D., *Chicago, Illinois*
H. HOUSTON MERRITT, *New York, New York*
E. P. RICHARDSON, JR., M.D., *Boston, Massachusetts*
RICHARD B. RICHTER, M.D., *Chicago, Illinois*
J. PRESTON ROBB, M.D., *Montreal, Canada*
AUGUSTUS S. ROSE, M.D., *Los Angeles, California*
ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*
A. EARL WALKER, M.D., *Baltimore, Maryland*
ROBERT WARTENBERG, M.D., *San Francisco, California*
PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.

Functional Disorders of the Cardiovascular System

Bellergal®

Stabilizer of the entire Autonomic Nervous System

Ergotamine tartrate	*0.3 mg.*
Bellafoline	*0.1 mg.*
Phenobarbital	*20.0 mg.*

Adult Dosage: 4 to 6 tablets daily.

SANDOZ

Sandoz
PHARMACEUTICALS
HANOVER, N. J.

Volume 5 **Neurology** *Number 7*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

JULY 1955 • *Contents*

Neurosurgical Experiences with Diabetes Mellitus 449
E. H. BOTTERELL, M.D. AND W. J. HORSEY, M.D.

Sensory Changes in the Upper Limb During Ischemia in Tetany..... 461
P. K. ROBINSON, M.B., M.R.C.P.

S. Weir Mitchell on Gunshot Wounds and Other Injuries of Nerves ...468
DAVID J. LA FIA, M.D.

The Hypothalamic Syndrome in Rats with Experimental Lesions..... 472
LEO C. MASSOPUST, JR., Ph.D.

Ballism Associated with Partial Destruction of the Subthalamic Nucleus of Luys 479
MALCOLM B. CARPENTER, M.D.

Swelling of Damaged Brain Tissue 490
RICARDO F. S. EDSTROM, M.D. AND HIRAM E. ESSEX, Ph.D.

Treatment Review

Diagnosis and Surgical Therapy of Chronic Midline Cervical Disk Protrusions 494
ERIC T. YUHL, M.D., DUKE HANNA, M.D., THEODORE RASMUSSEN, M.D. AND RICHARD B. RICHTER, M.D.

(Continued on next page)

NEUROLOGY, copyright 1955 by LANCET PUBLICATIONS, INCORPORATED. Title registered United States Patent Office. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. 84 South Tenth Street, Minneapolis 3, Minnesota. ADVERTISING REPRESENTATIVE: *New York 17:* Lee Klemmer, Bernard A. Smiler, John Winter, 50 East 42nd Street. Telephone: Murray Hill 2-8717. *Chicago 6:* Jay H. Herz, Hugh Gibson, 20 North Wacker Drive, Suite 1921. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., Mills Building. Telephone: Garfield 1-7950. *Los Angeles 5:* Duncan A. Scott & Co., 2978 Wilshire Blvd. Telephone: Dunkirk 8-4151.

Contents — *Continued*

Clinical Pathologic Conference 510

Presented by D. DENNY-BROWN, M.D. AND J. M. FOLEY, M.D.

Case Reports

Post-Seizure Purpura of the Head and Neck 516

THOMAS C. GUTHRIE, M.D.

Ectopic Pinealoma 518

RALPH L. DRAKE, M.D., BERT E. STOFER, M.D. AND LARRY VIN ZANT, M.D.

Calcified Subdural Hematoma 520

J. ARTHUR MAC LEAN, M.D. AND LAURENCE F. LEVY, M.B.

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D.C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis, Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

...you can help steady these hands

A simple matter to deal a pack of cards? Perhaps. But for the parkinsonian patient, easy tasks are often monumental. Helpless tremor mars his actions, damps his spirit.

You can effectively relieve the symptoms of Parkinson's disease in many patients with Parsidol. "Tremor alone responds best of all,"[1] and spasm, akinesia, festination, oculogyric crises, have all been controlled in a significant number of cases.[2, 3]

Parsidol is administered orally, either alone or with adjunctive therapy, such as atropine, scopolamine or stramonium.

PARSIDOL® HYDROCHLORIDE

(Brand of ethopropazine hydrochloride)

Available in

10 mg., 50 mg. and 100 mg. tablets, bottles of 100 and 500. Trial supplies and complete information on Parsidol will be sent promptly upon request.

Warner-Chilcott Laboratories
113 W. 18th St.,
New York 11, N. Y.

1. Palmer, H., and Gallagher, D. J. A.: Brit. M. J. 2:558 (Sept. 2) 1950. 2. Ziegler, D. K., and Torres, F.: Neurology 5:197 (March) 1955. 3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. 247:98 (July 17) 1952.

WARNER-CHILCOTT

Upjohn

Relax

the nervous,
tense,
emotionally unstable:

Reserpoid *(Pure crystalline alkaloid)*

TRADEMARK FOR THE UPJOHN BRAND OF RESERPINE

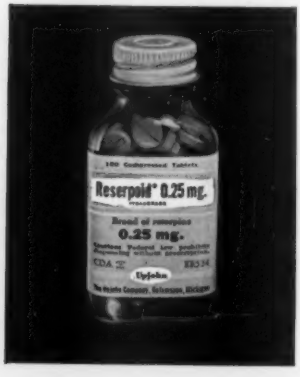
Each tablet contains:

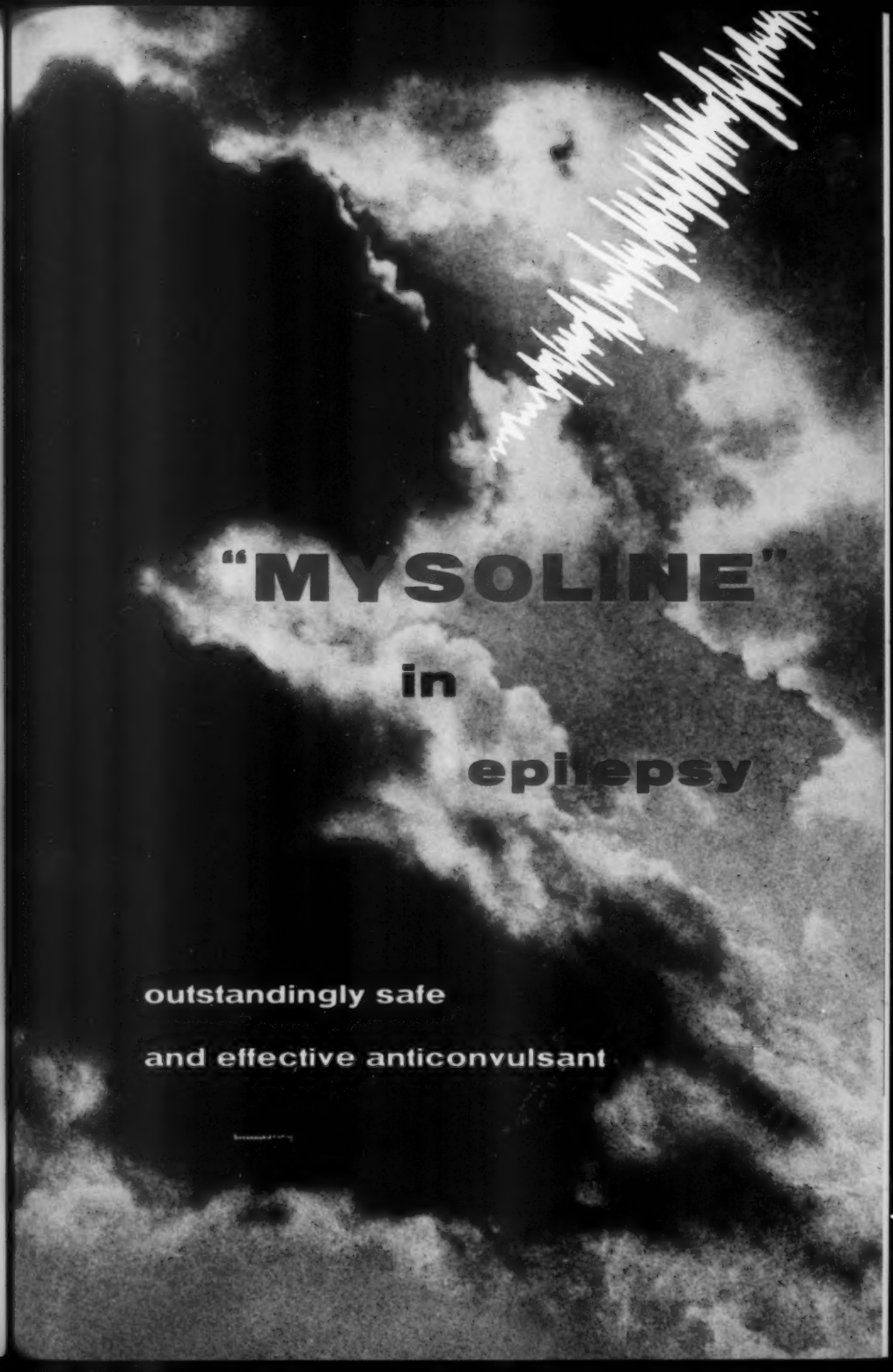
Reserpine ..... 0.1 mg.
or 0.25 mg.
or 1.0 mg.

Supplied:

Scored tablets
0.1 and 0.25 mg. in bottles of 100
and 500
1.0 mg. in bottles of 100

The Upjohn Company, Kalamazoo, Michigan




"MYSOLINE"
in
epilepsy
outstandingly safe
and effective anticonvulsant

Suggested dosage schedules for use of "Mysoline," employed alone, or in combination with other anticonvulsants.

Adults and children over 8 years: *In patients receiving no other anticonvulsants:* "Mysoline" therapy is started with 0.25 Gm. daily, and dosage is gradually increased at weekly intervals, until maximum therapeutic effect is achieved.

Order of Dosage Increase for Adults and Children Over 8 Years

1st week	2nd week	3rd week	4th week
0.25 Gm. (1 tablet) daily, at bedtime	0.5 Gm. (2 tablets) daily, 1 on arising, 1 at bedtime	0.75 Gm. (3 tablets) daily, in 3 divided doses	1 Gm. (4 tablets) daily, in 4 divided doses

When dosage is increased beyond 1 Gm., the daily intake is administered in four divided doses, and increments of 0.25 Gm. are added at weekly intervals as indicated above. Children 8 years and older are usually able to tolerate the same dosage as adults. ("Mysoline" is not recommended for use in dosages over 2 Gm. daily.)

In patients already receiving other anticonvulsants: "Mysoline," 0.25 Gm., is given daily and dosage is gradually increased, while the dosage of the other drug(s) is gradually decreased.

Children up to 8 years of age: 0.125 Gm. is administered on the same basis of therapy as suggested for adults. (In many cases control has been achieved with 0.375 Gm. to 0.75 Gm. daily.)

Supplied: No. 3430 – 0.25 Gm. tablets (scored). Bottles of 100 and 1,000.

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

1. Smith, B., and Forster, F. M.: Neurology *4*:137 (Feb.) 1954. • 2. Editorial: Brit. M. J. *1*:1028 (May 1) 1954. • 3. Lambros, V. S.: Read before the Annual Meeting of the American League Against Epilepsy, Washington, D. C., May 1, 1954. • 4. Smith, B. H., and McNaughton, F. L.: Canad. M.A.J. *68*:464 (May) 1953. • 5. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953. • 6. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

"MYSOLINE"®

Brand of Primidone

in epilepsy

"... comes closest to being an all purpose anticonvulsant ..."[1]

"... most convincingly effective in grand mal ..."[2]

"... may prove more beneficial than most drugs used for the psychomotor group ..."[2]

COMPLETE CONTROL OF SEIZURES IN 80 PER CENT OF PATIENTS WITH GRAND MAL

Lambros[3] reports that with "Mysoline," complete control of all attacks was achieved in 168 of 208 previously untreated patients with major seizures; in 14, partial control was obtained, this representing a reduction of 80 per cent in the frequency and severity of seizures.

FAVORABLE RESPONSE IN OVER 37 PER CENT OF REFRACTORY CASES

Smith and McNaughton,[4] using "Mysoline" in a group of 66 patients who had responded poorly or not at all to other anticonvulsants available, report that of 61 cases evaluated, over 37 per cent had most of their attacks reduced by half or more. More than half the patients had experienced seizures for more than 10 years, and 10 had had seizures for over 30 years.

NO SERIOUS SIDE REACTIONS IN 100 CASES

Doyle and Livingston note that in 100 epileptic patients on "Mysoline," no serious toxic reactions occurred. "Routine urine examinations and blood counts were made on every patient and showed no abnormality at any time." Side effects such as drowsiness and minor disturbances of equilibrium, when they occurred, "disappeared spontaneously in the majority of the patients within a few weeks after their onset."[5]

A detailed abstract of an important report on "Mysoline" is presented overleaf. A reprint of this report as well as literature providing an extensive bibliography will be sent to you on request.

Electroencephalogram showing typical wave pattern of a patient with grand mal seizures.

"MYSOLINE" PRODUCED COMPLETE CONTROL OF SEIZURES IN 71 PER CENT OF PATIENTS WHO HAD FAILED TO RESPOND TO OTHER MEDICATION.[6]

Pence's[6] report covers 45 patients ranging in age from 3 to 58 years who were observed for a period of 6 to 26 months. Cases of grand mal, petit mal, focal seizures, and psychomotor epilepsy were included in this series.

"Mysoline" was gradually added to current medication which in turn was gradually reduced during a two week period. The dosage ranged from 0.25 Gm. to 2.25 Gm. daily.

Results of therapy: Excellent results were obtained in 71 per cent of patients (32); improvement was noteworthy in 22 per cent (10); only 7 per cent (3) were not benefited.

The greatest improvement was noted in the 19 patients with grand mal, 16 being completely controlled. These patients received "Mysoline" alone or in combination with phenobarbital or a hydantoin.

The 2 patients with psychomotor attacks became completely controlled with "Mysoline" alone. Marked improvement was also noted in 9 of the 12 patients with petit mal.

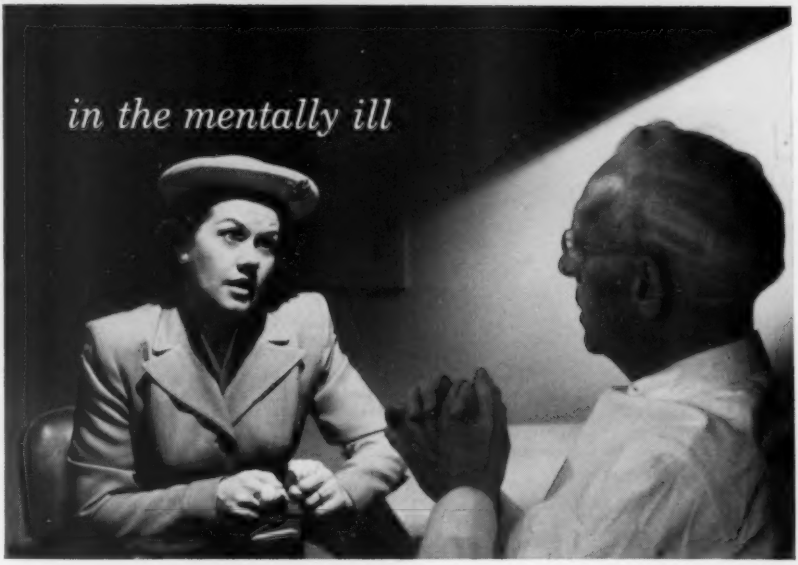
Pence points out that many patients were "well pleased with the results obtained when 'Mysoline' was substituted for all or part of their previous medication." Improvement in mental alertness was also noted with "Mysoline" therapy.

Side reactions: Urinalyses and blood counts remained normal; no skin rash was noted. When side effects such as drowsiness and ataxia occurred, they disappeared after the proper dosage of "Mysoline" was established.

"MYSOLINE"®

in epilepsy

Ayerst Laboratories make "Mysoline" available in the United States by arrangement with Imperial Chemical (Pharmaceuticals) Limited. 5563



'Sandril'

(RESERPINE, LILLY)

. . . *facilitates psychiatric treatment*

'Sandril' calms, diminishes anxiety and tension, improves sleep pattern in psychoneurotic states.

'Sandril' frequently produces relaxation, decrease in hallucinations and delusions, improved communication, and increased depth of effect in psychotic patients. Raging, combative, unsociable patients usually become more co-operative, friendlier, quieter, and much more amenable to psychotherapy and rehabilitation measures.

'Sandril' is virtually nontoxic; does not produce liver damage or severe orthostatic hypotension.

Lilly

QUALITY / RESEARCH / INTEGRITY

DOSAGE: Usually 0.5 to 1 mg. twice daily.

SUPPLIED: Tablets, 1 mg., yellow (scored), in bottles of 100 and 1,000. Also, tablets, 0.1 mg., orange, and 0.25 mg., green (scored); elixir, 0.25 mg. per 5 cc.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

Lederle

Hibicon*

Benzchlorpropamide *Lederle*

IN GRAND MAL AND PSYCHOMOTOR EPILEPTIC SEIZURES

HIBICON is a potent anticonvulsant which does not require reinforcement with sedatives. It is practically non-toxic, and patients are slow to develop a tolerance for it. It effects a feeling of well-being and heightened morale, without causing lethargy. The usual dosage is 0.5 Gm. to 1.5 Gm., 3 or 4 times daily, with meals and before retiring.

HIBICON is supplied in 250 mg. and 500 mg. capsules, in bottles of 100 and 1,000.

*REG. U.S. PAT. OFF.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
PEARL RIVER, NEW YORK

Serpasil®

EFFECTIVE EMOTIONAL STABILIZER WHEN USED IN ADEQUATE DOSAGE

IF adequate doses of Serpasil are given, many neuropsychiatric patients can be emotionally stabilized, as shown in a recent study.[1]

These doses may be considered high when compared with those used in the treatment of anxiety states and hypertension, but they are absolutely required and generally well tolerated.

1. Noce, R. H., Williams, D. B., and Rapaport, W.: J.A.M.A. *156*:821 (Oct.) 1954.

If you do not have a dosage card, please clip out plan below.

2/2083M

Serpasil

DOSAGE PLAN FOR NEUROPSYCHIATRIC CONDITIONS

Serpasil in doses of 2.5 to 5.0 mg. (1 to 2 ml.) is administered intramuscularly, while oral medication is started at 1.0 mg. b.i.d. It may be necessary to repeat the injection every day or every other day for the first 2 or 3 weeks. After the first week, the oral dosage may be increased, when necessary, to three or four 1.0-mg. tablets per day. As a general rule, a maintenance dosage of one to two 1.0-mg. tablets daily is adequate after a few weeks of therapy.

SERPASIL®
(reserpine CIBA)

CIBA
SUMMIT, N. J.

Parenteral Solution (for psychiatric use only),
2.5 mg. Serpasil per ml., 2-ml. ampuls.

Tablets,
1.0 mg. (scored), 0.25 mg. (scored), 0.1 mg.

Elixir,
0.2 mg. Serpasil per 4-ml. teaspoonful.

Upjohn

Relax

the nervous, tense, emotionally unstable:

Reserpoid *(Pure crystalline alkaloid)*

TRADEMARK FOR THE UPJOHN BRAND OF RESERPINE

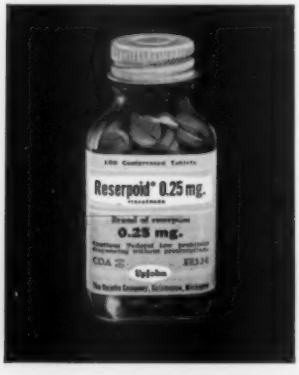
Each tablet contains:

Reserpine ..... 0.1 mg.
or 0.25 mg.
or 1.0 mg.

Supplied:

Scored tablets
0.1 and 0.25 mg. in bottles of 100 and 500
1.0 mg. in bottles of 100

The Upjohn Company, Kalamazoo, Michigan



Cogentin®

METHANESULFONATE (BENZTROPINE METHANESULFONATE, MERCK) (TROPINE BENZOHYDRYL ETHER METHANESULFONATE)

rated the best single drug in parkinsonism[1]

MAJOR ADVANTAGES: Effective against rigidity.[2] Counteracts muscle spasm.[3] "Good against major tremor."[3] "Safe."[2]

COGENTIN helps control palsied hands—often with a single daily dose

COGENTIN affords maximal symptomatic relief in parkinsonism – whether postencephalitic, idiopathic or arteriosclerotic.

For alleviating *spasm* and *cramps, rigidity* and *contracture* of parkinsonism, COGENTIN is "better than any drug currently available."[4]

Severe tremor, unaffected by standard medication, improved in many cases when COGENTIN was given.[5]

COGENTIN is reported to be *safe* in all forms of parkinsonism[2] Even the elderly tolerate it well.[5] It "does not cause drowsiness" or similar side effects during the day.[4]

Dosage: Effective symptomatic relief may usually be obtained with a single 1 or 2 *mg.* dose taken orally before retiring. Each quarter-scored tablet contains 2 *mg.* COGENTIN.

References: 1. M. Clin. North America 38:485 (March) 1954. 2. Neurology 2:233 (May-June) 1952. 3. J.A.M.A. 156:680 (Oct. 16) 1954. 4. Parkinsonism and its Treatment, Phila., J. B. Lippincott Co., 1954, pp. 87-88. 5. Neurology 3:361 (May) 1953.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

THORAZINE*

Shortens Duration of Psychotic Attacks

"A 50% reduction in the probable duration of a psychotic attack may be expected with ['Thorazine'] in psychotic breakdown characterized by psychomotor excitement or emotional tension."

Patients "recover with ['Thorazine'] within an unusually short time without the help of insulin coma or electroconvulsive therapy".

Furthermore, "the patient's insight is often better because amnesia and confusion do not develop under treatment".

Lehmann, H.E.: Canad. M. A. J. *72*:91 (Jan. 15) 1955.

'Thorazine' Hydrochloride is available in 10 mg., 25 mg., 50 mg. and 100 mg. tablets; 25 mg. (1 cc.) and 50 mg. (2 cc.) ampuls; and syrup (10 mg./5 cc.).

Additional information on 'Thorazine' is available on request.

Smith, Kline & French Laboratories
1530 Spring Garden Street, Philadelphia 1

*T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of chlorpromazine.

Volume 5 Neurology *Number 7*

Neurosurgical Experiences with Diabetes Insipidus

E. H. Botterell, M.D. and W. J. Horsey, M.D.

DIABETES INSIPIDUS is encountered rather infrequently in neurosurgical practice, but when present it is often of diagnostic importance. The clinical picture is well known. The unfortunate victim is so preoccupied with the necessity of drinking large quantities of fluid and of voiding comparable volumes of urine, that he has little time for other forms of activity. Sleeplessness and fatigue add to his burden of complaints.

PHYSIOLOGY OF WATER EXCRETION

Investigations of renal function[44] have shown that the various parts of the nephron are concerned with different phases of urinary excretion. The glomerular filtrate is a virtually protein-free solution of electrolytes, glucose, and urea. The rate of filtration in man is about 127 cc. per minute (1.73 sq.m.adult). Approximately 85 per cent of the water of the filtrate is reabsorbed passively in the proximal convoluted tubule and in the thin segment of Henle's loop, leaving 20 cc. per minute of fluid, isotonic with the plasma, to enter the distal tubule. Here it is further concentrated, to a varying degree, determined by the state of hydration of the individual. Usually the rate of flow of urine is about 1 cc. per minute, indicating that 19 cc. of water are absorbed in the distal segment.

The reabsorption of water in the distal tubule is regulated hormonally by the neurohypophysis, which in turn is under the influence of the hypothalamus. The neurohypophysis[38] comprises the infundibular process (neural lobe), the infundibular stem, and the median eminence of the tuber cinereum. These structures have an identical histologic appearance, characterized by the presence of unmyelinated nerve fibers and pituicytes, the parenchymal cells of the

From the department of surgery, University of Toronto, and the neurosurgical division of the Toronto General Hospital, Toronto, Ontario.

neurohypophysis. It has been shown repeatedly that extracts of the neural lobe contain a biologically active antidiuretic principle (pitressin, A.D.H.). Pitressin has no direct effect upon the elimination of sodium or chloride, and produces only a very slight secondary reduction in the excretion of sodium ion when the rate of urinary flow is reduced to less than 1 cc. per minute.[10,23,32]

This concept of facultative reabsorption is at variance with that advanced by Trueta and his co-workers[47] who believe that the action of pitressin is not on the distal tubule, but on the renal vascular bed, diverting blood from the peripheral cortical nephrons to those in the juxtamedullary zone. The latter, with their long thin segments in Henle's loop, are thought to be more efficient in the reabsorption of water.

The unmyelinated fibers of the neurohypophysis have their origin in the anterior hypothalamus, arising in the paired supraoptic and paraventricular nuclei.[16] The supraoptic nuclei contribute the vast majority of the fibers and, in so far as it is known, are the only nuclei concerned with the hormonal regulation of the excretion of water. Rasmussen[36] estimated that in man each supraoptic nucleus comprises about 60,000 cells whose axons pass posteroinferiorly in the well defined supraopticohypophyseal tract. The histologic appearance of these cells and their highly vascular bed suggest that the nuclei may have a secretory function.[11,15,40]

Verney[49] showed in the dog that one adequate stimulus for the elaboration of the antidiuretic hormone is an increase in the osmotic pressure of the blood delivered into the internal carotid artery. Painful stimulation and emotional disturbances inhibit water diuresis, even if the kidneys are denervated, indicating a hormonal rather than reflex influence upon the process.[45,46] Liberation of the antidiuretic principle is increased by acetylcholine[9] and nicotine[8,51] and is decreased by alcohol.[48] The hormone is eliminated in the urine. Gilman reports that in dehydration the amount excreted is increased, whereas in the presence of an adequate supply of water it is reduced.[18] Harris found that electrical stimulation of the supraoptic nuclei leads to the elaboration of pitressin.[20]

PATHOPHYSIOLOGY OF DIABETES INSIPIDUS

It has been demonstrated experimentally in the cat and the monkey that lesions of the hypothalamohypophyseal system produce diabetes insipidus.[16] Following interruption of the supraopticohypophyseal tracts in animals and in man, the neurons of the supraoptic nuclei degenerate and atrophy of the neurohypophysis ensues.[16,36,37] Neural control over the liberation of pitressin is lost. The hormone is not elaborated in adequate quantities to promote facultative reabsorption of water, and the subject excretes excessive amounts of urine of low specific gravity. Secondarily, polydipsia is evident. The glomerular filtration rate and the renal plasma flow are reduced by about 50 per cent, due to a presumed cessation of activity of many nephrons in an attempt to conserve water.[19] The total soluble excretion is practically unchanged. Experimental diabetes insipidus is readily controlled by parenteral injection of pitressin.

If the supraopticohypophyseal tract of a cat is destroyed completely, transient diabetes occurs immediately and is followed by a return to the normal rate

of urine flow usually within five days. Maximal permanent diabetes insipidus appears after a latent period of about ten days. If the neurohypophysis is entirely ablated, maximal permanent diabetes occurs without delay.[16] This fact suggests that the latent period is due to the continued liberation of stored hormone by the denervated but still undegenerated gland in the former circumstance. If as much as 5 per cent of the hypothalamohypophyseal system remains intact, diabetes is permanent but subtotal, amounting to four or five times the normal output. If 15 per cent remains in function, the diabetes is transient and subtotal.[21]

The role of the adenohypophysis in the hormonal regulation of the excretion of water has been the subject of much study.[17,44] There is considerable controversy but the weight of experimental evidence indicates that maximal dibetes insipidus does not occur unless at least a portion of the pars glandularis is active. It is of interest that Shimkin and associates[41] and Luft and Olivecrona[30] do not mention diabetes insipidus in their reports on hypophysectomy in man. In human cases, however, the whole of the neurohypophysis is not removed and in many a very small portion of the adenohypophysis may be left behind. Smith[44] believes that the adenohypophysis may elaborate a renotrophic factor, in the absence of which glomerular filtration rate is reduced.

Although thyroidectomy has no effect upon the water metabolism of normal subjects, removal of the thyroid gland diminishes the severity of the polyuria in diabetes insipidus.[14,16] It has been suggested that the pars glandularis influences urinary excretion by some mechanism involving the thyroid gland.

CLINICAL DIAGNOSIS

The clinical diagnosis of diabetes insipidus is based upon the presence of an obligatory polyuria not associated with renal disease or diabetes mellitus. Corresponding polydipsia, now conceded to be secondary to dehydration,[24] is often so severe that thirst is agonizing if fluids are withheld. Copious quantities of pale dilute urine of low specific gravity (1.000 to 1.009) are excreted even when attempts are made to restrict the intake of water. The rate of flow is not absolutely fixed, probably due to variations in the osmotic load[4] and, in some subtotal cases, to fluctuation in the severity of deprivation of antidiuretic hormone. The response of true diabetes insipidus to the administration of pitressin is striking, both in the diminution of the production of urine and in the elevation of its specific gravity. Subtotal diabetes is seen more frequently than total diabetes in man.

The most difficult point in the diagnosis is the differentiation from psychogenic polydipsia. The presence of an antidiuretic response to intravenous infusions of hypertonic saline[6] and to nicotine[5,17] may be of some assistance in excluding the functional cases when restriction of fluids is not well tolerated.

CLINICAL MATERIAL

In the records of the Toronto General Hospital, there are 22 well-documented cases of diabetes insipidus. No search was made for cases not coded under this diagnosis. The causative factors in the cases were as follows:

Trauma	7 cases
Tumor	2 "
Sarcoidosis	1 "
Undetermined	12 "
Total	22 cases

It is remarkable that many causes frequently noted in the current literature do not occur in this group, for example, syphilis,[26] sphenoidal sinusitis,[1] xanthoma,[26,29] encephalitis,[26] and ectopic pinealoma.[25]

POSTTRAUMATIC DIABETES INSIPIDUS

In the Toronto General Hospital series, six cases followed accidental injury and one occurred postoperatively. In addition, one case was available for study in the records of the Toronto Western Hospital and the division of neuropathology, department of pathology, University of Toronto.

Case 1.—An 18 year old boy was injured in a truck accident on October 16, 1952. He sustained a linear fracture of the base of the skull, but no basal fracture was seen on x-ray examination. On October 21 an extradural hematoma was evacuated. Thirteen days following injury, his urinary output began to rise dramatically. His daily urine volume reached 13,700 cc. and was accompanied by a fluid intake equally great. The specific gravity of his urine fell from 1.012 to 1.001. The 24 hour exchange of fluids was reduced to less than 2,500 cc. by the intramuscular injection of 1 cc. of pitressin tannate in oil every three days. The patient continued to require hormone therapy, and when seen seven months after injury he was taking a 1 cc. injection weekly.

Final diagnosis: Craniocerebral injury; fracture of skull; extradural hematoma; posttraumatic diabetes insipidus.

Case 2.—Following an automobile accident on May 16, 1948, an 18 year old boy was unconscious for about seven days. Recovery was impeded by pulmonary atelectasis. Bleeding from the left external auditory canal and retromastoid ecchymosis indicated a fracture of the base of the skull, although this could not be visualized on x-ray examination.

Eight days after injury, it was noted that the specific gravity of the urine had fallen from a previous level of 1.024 to 1.004. The fluid exchange exceeded 10,000 cc. in 24 hours. With the subcutaneous injection of 1 cc. of pitressin in aqueous solution every eight hours, the specific gravity rose to 1.013 and the daily intake and output of fluid fell to approximately 3,600 cc. Hormone therapy was discontinued after two months, although thirst and urinary frequency were still a little excessive. By October 15, 1948, he had no complaints. He has remained well. A random sample of urine examined in May 1953 showed a specific gravity of 1.020.

It is noteworthy that this patient gained approximately 60 pounds in weight during the five months following his craniocerebral injury. Subsequently this weight was lost. He claims that he made no attempt to follow a diet, that he recognized no change in his appetite, and that the amount of physical activity once he left hospital was about constant.

Final diagnosis: Craniocerebral injury; fracture of the base of the skull; pulmonary atelectasis; posttraumatic diabetes insipidus.

Case 3.—Three days after a relatively mild head injury in June 1942, when he fell from a ladder, a 42 year old man noted the onset of polyuria and polydipsia. Physical examination at the time revealed no neurologic deficit, and x-rays of the skull showed no fracture. He voided as much as ten liters of urine daily. Gradually his bladder capacity increased, so that he could hold 1,000 cc. without discomfort. Intense thirst and voluminous urinary excretion persisted.

When first seen at the Toronto General Hospital in March 1951, the specific gravity of the urine was 1.001 and the exchange of fluids as much as 7,500 cc. daily. The diabetes insipidus was controlled with 0.5 cc. of pitressin tannate in oil injected intramuscularly every three days.

Final diagnosis: Posttraumatic diabetes insipidus.

Case 4.—In an automobile accident on August 8, 1953, a 62 year old woman sustained a craniocerebral injury with craniofacial separation and facial lacerations. At the same time numerous ribs and the left ulna were broken. X-rays of the skull showed no fracture except those of the face; the vault and base were normal. Eight days after injury a subdural hygroma was evacuated. Her level of consciousness, poor until this time, began to improve and thereafter she made steady progress.

Between August 16 and August 26, her daily exchange of fluids was about 7,300 cc. daily. She complained constantly of intense thirst and urinary frequency. The specific gravity of the

urine was 1.001. The blood nonprotein nitrogen was 35 mg. per 100 cc.

With 0.5 cc. of pitressin tannate in oil given intramuscularly every 12 hours, the polyuria and polydipsia subsided. The daily intake and output fell to 870 cc. and the urinary specific gravity rose to 1.007. At first she complained of nausea and vomiting following the injections, but within a few days of commencing therapy she had no side effects.

Final diagnosis: Craniocerebral injury; subdural hygroma; craniofacial separation; facial lacerations; posttraumatic diabetes insipidus; fractured ribs (bilateral); fracture of left ulna.

Case 5.—A 35 year old man was struck by an automobile on December 31, 1948. He suffered a severe craniocerebral injury, with fractures of the left parietal and temporal bones. There were also fractures involving the frontal, ethmoidal, and sphenoidal sinuses. Bleeding from the nose, mouth, and left ear was considerable. A leak of cerebrospinal fluid from the left nostril persisted for about two weeks. There was a Horner's syndrome on the left side and paresis of the left external rectus muscle.

He was comatose for about 48 hours. When he regained consciousness there was severe dysphasia and intellectual impairment. During the ensuing months he improved so that he could resume his former occupation as vice-president of a printing company one year later.

Approximately two weeks after the injury, the patient complained of persistent thirst and it was noted that he was voiding a large volume of urine. The greatest 24-hour intake of fluid was recorded as 9,070 cc. while the maximum urinary output was 8,880 cc. The polyuria and polydipsia subsided gradually during March 1949.

Final diagnosis: Craniocerebral injury; cerebral contusion; posttraumatic dysphasia; fracture of temporal and parietal bones; fracture of frontal, ethmoidal, and sphenoidal sinuses; cerebrospinal fluid rhinorrhea; posttraumatic diabetes insipidus.

Case 6.—On August 20, 1949, a 17 year old girl sustained a fracture dislocation of the neck (C6-C7) in an automobile accident. She was thrown forward from the rear seat, striking her face against the back of the front seat. She was rendered quadriplegic immediately. She was not unconscious. X-ray examination showed no fracture of the skull. Several days after injury, she was voiding large quantities of dilute urine and drinking excessively. On transfer to the Toronto General Hospital on September 15, 1949, she was dehydrated but in spite of this the specific gravity of the urine was 1.002. Since the polyuria was subsiding, the maximum 24-hour volume recorded was 4,600 cc., with the greatest fluid intake 5,500 cc. She did not receive pitressin. She returned to a hospital near her home where she died in December 1949. Autopsy was not carried out.

Final diagnosis: Fracture dislocation of the cervical spine (C6-C7), quadriplegia; craniocerebral injury—mild; posttraumatic diabetes insipidus.

Case 7.—A 54 year old man was brought to the Toronto Western Hospital on March 10, 1945, shortly after sustaining a severe craniocerebral injury. He survived in hospital for a period of nine hours, but during a two and a half hour period he excreted 900 cc. of pale urine.

Postmortem examination revealed a fracture of the vault of the skull, but no fracture of the base. A recent hemorrhage was found in a cystic space in the infundibular process of the hypophysis (figure 1).

Final diagnosis: Craniocerebral injury, severe; fracture of the vault of the skull; hemorrhage into neurohypophysis; posttraumatic diabetes insipidus.

Case 8.—A 24 year old man had a left frontotemporal craniotomy on August 11, 1952, for the removal of a large epidermoid cyst which had caused a right homonymous upper quadrantic visual field defect, left-sided anosmia, and epilepsy. The lesion extended from the left Sylvian fissure across the midline above the sella turcica. When the cyst was removed, the left internal carotid artery and some of its branches could be seen bridging the cavity which remained, and the right internal carotid artery was visualized in the depths of the tumor bed. During the operative procedure, the hypophyseal stalk was transected (figure 2).

Preoperatively the patient had no urinary complaints. However, during the first 12 hours following recovery from the general anesthesia, the volume of urine excreted was 9,900 cc. With the administration of A.D.H. the urinary output fell to normal. He required injections of 1 cc. of pitressin tannate in oil every two to

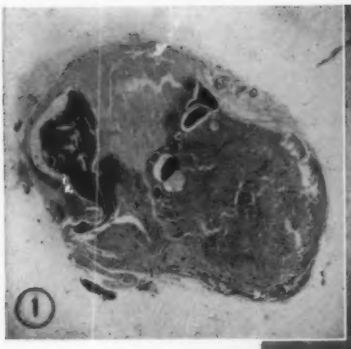


FIG. 1. Photomicrograph of a horizontal section through the hypophysis in case 7, showing a recent hemorrhage into a cystic space in the infundibular process.

FIG. 2. Photograph of the operative field in case 8 following removal of the tumor. Note the transected hypophyseal stalk, the cut end of which is projecting through the diaphragm sellae. The left internal carotid artery is bridging the space left by the removal of the lesion.

three days. When the therapy was omitted, polyuria and polydipsia appeared and the urine specific gravity fell to 1.001. It was possible to decrease the frequency of the injections gradually, so that he no longer needed replacement therapy one year after operation.

Final diagnosis: Intracranial epidermoid tumor—suprasellar; diabetes insipidus—postoperative.

DISCUSSION

During the six-year period from 1948 to 1953 inclusive, there were 1,148 patients admitted to the Toronto General Hospital with a diagnosis of craniocerebral injury. In this interval, five new cases of posttraumatic diabetes insipidus were recognized during the period of hospitalization, an incidence of 0.44 per cent. It is of interest that in the five-year period preceding 1948, there were 570 cases of head trauma with no cases of posttraumatic diabetes insipidus discovered. Warkany and Mitchell[52] quote Zenker, who reported in 1919 four patients with diabetes insipidus in 2,800 cases of head injury, an incidence of 0.14 per cent. There are available no recently published statistics indicating the frequency of this complication of craniocerebral trauma, although many authors emphasize its rarity.[34,39,50] Nevertheless,

it is the most common sequel of hypothalamic damage in those surviving head injury.

In many instances the mechanism of production of posttraumatic diabetes insipidus is probably traction on the pituitary stalk as the brain moves violently within the cranial cavity.[22,35] Alternatively, hemorrhage may take place in the neurohypophysis, as exemplified in case 7.

Basal skull fractures are sometimes observed, but they are by no means essential to the development of the syndrome.[33,34,50] Only two of the seven cases following accidental injury showed evidence of such a fracture.

With one exception (case 7), the cases of diabetes inspidus following accidental trauma showed a lag, ranging from three to several days, between the time of injury and the onset of symptoms. The average delay was about eight days in the four cases in which the interval was measured. The recorded latent period which precedes the onset of diabetes may be due to failure to recognize polyuria and polydipsia in an uncooperative, restless, or semicomatose patient who is incontinent and unable to request fluids. On the other hand, it may correspond to the delay in the development of diabetes insipidus following experimental lesions of the supraopticohypophyseal tract in animals, with the continued liberation of stored antidiuretic hormone by the denervated gland. It is noteworthy that the patient with hemorrhage into the neurohypophysis (case 7) had polyuria on the day of his injury. The course in this instance could be compared with that of animals in which the entire neurohypophysis is ablated, resulting in immediate total diabetes insipidus. The immediate appearance of diabetes inspidus in the patient whose hypophyseal stalk was transected at operation (case 8) is difficult to explain unless this phenomenon corresponds to the transient polyuria in the experimental animal with a lesion in the supraoptic nucleus or infraopticohypophyseal tract.

According to most authors, the prognosis in posttraumatic diabetes insipidus is good, provided that the patient survives the injury and its other complications.[34,39] Nevertheless, the condition may persist indefinitely, as exemplified in case 3 in this series. Restoration of hypothalamohypophyseal function may follow resorption of hemorrhage and edema, or it may depend upon hypertrophy or adaptation of that portion of the neurohypophysis not destroyed by injury.

DIABETES INSIPIDUS DUE TO SPACE-OCCUPYING LESIONS

Two cases of diabetes insipidus were due to new growths involving the hypothalamohypophyseal system. A third was caused by sarcoidosis.

Case 9.—An 18 year old girl had a suprasellar adamantinoma which caused headache, papilledema, and failing vision. Partial removal of the tumor on August 8, 1942 resulted in improvement in vision and reduction of headaches and papilledema. In December 1942 she noted an increase in the frequency of micturition. She ceased menstruating and became very obese, gaining 80 pounds. Visual acuity deteriorated again. On April 28, 1943 she was readmitted to hospital. At that time the specific gravity of her urine varied between 1.000 and 1.007. The 24-hour fluid intake was as high as 4,180 cc. while the output was 5,930 cc. Following the injection of pitressin tannate in oil, the daily intake fell to 725 cc. and the output to 1,150 cc. The specific gravity of the urine rose to 1.038.

The girl succumbed after a second craniotomy. At autopsy the tumor was seen compress-

ing the hypothalamus and extending into the sella turcica.

Final diagnosis: Suprasellar adamantinoma; diabetes insipidus.

Case 10.—A 45 year old man noted the sudden onset of polydipsia and polyuria in June 1945. He claimed that excessive thirst preceded the increased urinary output. His complaints became worse. He began to vomit. On December 29, 1945 he was admitted to the Toronto General Hospital. Physical examination revealed a dehydrated, emaciated man. The visual fields were full. Skull x-rays were normal. The output of urine varied between 3,300 cc. and 8,700 cc. in 24 hours, while the intake ranged from 4,500 cc. to 10,460 cc. The specific gravity of the urine fluctuated between 1.001 and 1.004. With daily subcutaneous injections of surgical pituitrin, the exchange of fluid rarely rose above 3,000 cc. in 24 hours. The specific gravity of the urine reached 1.008. For a month prior to death on May 5, 1946, he was listless and somnolent. Autopsy showed a scirrhous carcinoma of the stomach which had metastasized to the pituitary gland. The neural lobe was almost entirely replaced by tumor (figure 3). Carcinoma had also invaded the pars distalis. The hypothalamus was not involved.

Final diagnosis: Scirrhous carcinoma of stomach; metastatic carcinoma of pituitary gland; diabetes insipidus.

Case 11.—In 1939 a 45 year old man had polyuria and polydipsia controlled by injections of pituitrin. Without medication, he voided 15 times daily and eight times nightly. These complaints gradually subsided, but in 1945 they recurred for no apparent reason. Weakness and pain in the legs followed. He was admitted to the Toronto General Hospital on September 27, 1945. At that time obesity, fine skin texture, and a peculiar distribution of body hair suggested a female habitus. Perimetry revealed a bitemporal visual field defect. The cerebrospinal fluid contained 32 lymphocytes per cu. mm.; the total protein was 250 mg. per 100 cc. Radiographic study of the chest showed minute scattered areas of infiltration in both lung fields. The specific gravity of the urine was 1.006. No pitressin was given. He lost weight and finally died on October 15, 1945.

At autopsy the lungs and mediastinal lymph nodes were riddled with sarcoid tissue, evident on gross and microscopic examination. In addition, the hypothalamus was infiltrated with identical tissue, seen on gross and histologic study (figure 4). The hypophysis was normal.

Final diagnosis: Sarcoidosis of hypothalamus, mediastinal lymph nodes, and lungs; diabetes insipidus.

DISCUSSION

These three cases of diabetes insipidus illustrate three different methods whereby space-occupying lesions may produce the syndrome: 1) compression of the hypothalamus and hypophysis; 2) replacement of the neurohypophysis by tumor tissue; and 3) invasion of the hypothalamus.

It is of interest that Cushing[12] recognized these mechanisms of production of clinical diabetes insipidus before Fisher and his associates[16] published their conclusions drawn from animal experimentation.

DIABETES INSIPIDUS DUE TO UNDETERMINED CAUSES

Since 1929 there have been in the Toronto General Hospital, 12 cases of diabetes insipidus in which the cause of the syndrome was not established.

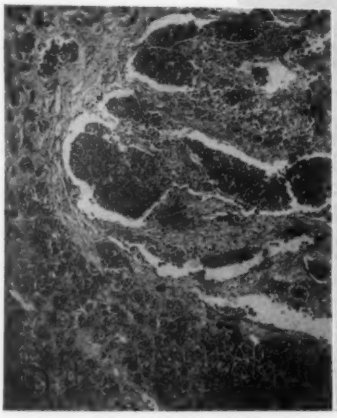
One of these, case 12, was a man who developed cerebellar ataxia and anosmia eight years after the onset of polyuria.

A woman of 74 years, case 13, with intense polydipsia and polyuria (14,000 cc. in 24 hours) gave a life-long history of these symptoms. In seven generations of her family there were 39 cases of diabetes insipidus among a total of 78 individuals. She died in a state of hyperthyroidism.

Two patients (cases 14 and 15) gave a history compatible with a diagnosis of encephalitis prior to admission. However, the physical findings and cerebrospinal fluid examination in hospital did not confirm this clinical impression.

FIG. 3. Photomicrograph of a horizontal section through the hypophysis in case 10, showing extensive infiltration of the infundibular process by metastatic carcinoma. The pars distalis is also involved.

FIG. 4. Midsagittal section of brain in case 11, showing thickening of hypothalamus due to sarcoidosis.



In the remaining cases, there was no suggestion of an etiologic factor. Coincidentally, one had an essential hypertension and one had chronic pyelonephritis.

ASSOCIATED DYSFUNCTIONS

Associated dysfunctions attributable to lesions in the region of the hypothalamus were observed in five instances. Four of these were in persons with verified intracranial space-occupying lesions. Two were somnolent for approximately one month before death (cases 10 and 11). Three had visual field defects due to involvement of the extracerebral portions of the visual pathways (cases 8, 9, and 11). Anosmia was noted twice (cases 8 and 12). Obesity was seen on two occasions (cases 2 and 9). In the posttraumatic case (case 2) the obesity was transient. Endocrine disturbance, in the form of amenorrhea, was observed in case 9.

THERAPY

The removal of tumors from the suprasellar region and from the pituitary fossa often fails to control diabetes. The most effective management is to give pitressin in amounts sufficiently large to meet the requirement of the individual. All patients receiving pitressin in the present series were noticeably improved. It is available as pitressin tannate in oil, an extremely reliable preparation for intramuscular injection. The effects of one injection may last many days. The benefits of injections of aqueous solutions are evanescent. Posterior pituitary powder is the most convenient form in which the hormone may be taken,[3,7,13,43] permitting the patient to regulate dosage according to his requirements. It is possible that a patient who receives pitressin may continue to drink large quantities of water and so precipitate water intoxication.

Thyroidectomy[2] and the oral administration of thiouracil derivatives[27] have been employed on the basis that experimental diabetes insipidus is reduced in severity in the absence of thyroxin. These methods have not been sufficiently successful to justify their use in patients.

SUMMARY

The hypothalamohypophyseal system regulates the rate of excretion of water in the urine by the elaboration of the antidiuretic hormone (pitressin). Lesions of the supraoptic nuclei, of the supraopticohypophyseal tracts, or of the neurohypophysis are capable of causing diabetes insipidus in humans, and, experimentally, in animals. Polyuria and polydipsia are readily controlled by the parenteral administration of pitressin.

A series of patients with posttraumatic diabetes insipidus is described. The incidence of this complication is 0.44 per cent of 1,148 cases of craniocerebral injury admitted to the Toronto General Hospital in six years. Of seven cases following accidental injury, six developed symptoms after a latent period of about eight days (average), while one had polyuria on the day of injury. At autopsy, the latter showed a recent hemorrhage into a cystic space in the infundibular process of the neurohypophysis.

Three patients with intracranial space-occupying lesions are presented to show how the hypothalamohypophyseal system may be disorganized with the production of diabetes insipidus. Associated neurologic and endocrine disorders are described. The parenteral administration of the antidiuretic hormone conveniently and effectively controls the diabetes.

The authors' thanks are extended to Professor Linell and the department of neuropathology, University of Toronto, for permission to use figures 1, 3, and 4, and to Dr. C. W. Harris of the Toronto Western Hospital, and Professor Linell of the department of neuropathology, University of Toronto, for permission to include case 7.

REFERENCES

1. Ball, K. P., and Thackray, A. C.: Diabetes insipidus due to sphenoidal sinusitis: Report of a case, Lancet 1:637, 1948.
2. Blotner, H., and Cutler, E. C.: Total thyroidectomy in the treatment of diabetes insipidus, J.A.M.A. 116:2739, 1941.
3. Blumgart, H. L.: The antidiuretic effect of pituitary extract applied intranasally in a case of diabetes insipidus, Arch. Int. Med. 29:508, 1922.
4. Brodsky, W. A., and Rapoport, S.: The mechanism of polyuria of diabetes insipidus in man: The effect of osmotic loading, J. Clin. Investigation 30:282, 1951.
5. Burns, J. H.: Discussion: The diagnosis of diabetes insipidus, Proc. Roy. Soc. Med. 43:841, 1950.

6. Carter, A. C., and Robbins, J.: The use of hypertonic saline infusions in the differential diagnosis of diabetes insipidus and psychogenic polydipsia, J. Clin. Endocrinol. 7:753, 1947.
7. Carter, A. C., and Shorr, E.: The intranasal use of posterior pituitary powder in the treatment of diabetes insipidus: A reminder, J. Clin. Endocrinol. 7:828, 1947.
8. Cates, J. E., and Garrod, O.: The effect of nicotine on urinary flow in diabetes insipidus, Clin. Science 10:145-160, 1951.
9. Chalmers, T. M., and Lewis, A. A. G.: Stimulation of the supraoptico-hypophyseal system in man. Clin. Sc. 10:127, 1951.
10. Chalmers, T. M., Lewis, A. A. G., and Pawan, G. L. S.: The effects of posterior pituitary extracts on the renal excretion of sodium and chloride in man, J. Physiol. 112:238, 1951.
11. Craigie, E. H.: Measurements of vascularity in some hypothalamic nuclei of the albino rat, A. Res. Nerv. & Ment. Dis., Proc. 20:310, 1940.
12. Cushing, H. C.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932, 234 pp.
13. Feriozi, D., and Schneider, D.: Insufflation of posterior pituitary powder in childhood diabetes insipidus: Report of a case, M. Ann. District of Columbia 17:557, 1948.
14. Findley, T. Jr.: Thyroid-pituitary relationship in diabetes insipidus, Ann. Int. Med. 11:701, 1937.
15. Finley, K. H.: Angio-architecture of the hypothalamus and its peculiarities, A. Res. Nerv. & Ment. Dis., Proc. 20:286, 1940.
16. Fisher, C., Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-hypophyseal System, Ann Arbor, Edwards Bros. 1938, 212 pp.
17. Gersh, I.: Water metabolism: Endocrine factors, A. Res. Nerv. & Ment. Dis., Proc. 20:436, 1940.
18. Gilman, A., and Goodman, L.: The secretory response of the posterior pituitary to the need for water conservation, J. Physiol. 90:113, 1947.
19. Handly, C. A., and Keller, A. D.: Changes in renal functions associated with diabetes insipidus precipitated by anterior hypothalamic lesions, Am. J. Physiol. 160:321, 1950.
20. Harris, G. W.: Neural control of the pituitary gland. 1. The neurohypophysis, Brit. M. J. 2:559, 1951.
21. Heinbecker, P., and White, H. L.: Hypothalamico-hypophyseal system and its relation to water balance in the dog, Am. J. Physiol. 133:582, 1941.
22. Holbourn, A. H. S.: Mechanics of head injuries, Lancet 145:438, 1943.
23. Holland, B. C., and Stead, E. A., Jr.: Effect of Vasopressin (pitressin)-induced water retention on sodium excretion, Arch. Int. Med. 88:571, 1951.
24. Holmes, J. H., and Gregersen, M. I.: Origin of thirst in diabetes insipidus, Am. J. Med. 4:503, 1948.
25. Horrax, G., and Wyatt, J. P.: Ectopic pinealomas in the chiasmal region, J. Neurosurg. 4:309, 1949.
26. Jones, G. M.: Diabetes insipidus: Clinical observations in forty-two cases, Arch. Int. Med. 74: 81, 1944.
27. Kaye, E.: Treatment of diabetes insipidus with propylthiouracil: Report of a case, California Med. 74:205, 1951.
28. Lewis, A. A. G., and Chalmers, T. M.: A nicotine test for the investigation of diabetes insipidus, Clin. Sc. 10:137, 1951.
29. Lewis, A. A. G., and Smart, J.: Diabetes insipidus with honeycomb lungs: Presumed normcholesteraemic xanthomatosis, Proc. Roy. Soc. Med. 44: 166, 1951.
30. Luft, R., and Olivecrona, H.: Experiences with hypophysectomy in man, J. Neurosurg. 10:301, 1953.
31. Melville, E. V., and Hare, K.: Antidiuretic material in the supraoptic nucleus, Endocrinology 36:332, 1945.
32. Murphy, R. J. F., and Stead, E. A., Jr.: The effects of exogenous and endogenous posterior pituitary antidiuretic hormone on water and electrolyte excretion, J. Clin. Investigation 30:1053, 1951.
33. Patrick, A.: Diabetes insipidus following fractured skull, Brit. M. J. 2:689, 1931.
34. Porter, R. J., and Miller, R. A.: Diabetes insipidus following closed head injury, J. Neurol., Neurosurg. & Psychiat. 11:258, 1948.
35. Pudenz, R. H., and Shelden, C. H.: The lucite calvarium—A method for direct observation of the brain. II. Cranial trauma and brain movement, J. Neurosurg. 3:487, 1946.
36. Rasmussen, A. T.: The effects of hypophysectomy and hypophyseal stalk resection on the hypothalamic nuclei of animals and man, A. Res. Nerv. & Ment. Dis., Proc. 20:245, 1940.
37. Rasmussen, A. T., and Gardner, W. J.: The effects of hypophyseal stalk resection on the hypophysis and hypothalamus of man, Endocrinology 27:219, 1940.
38. Rioch, D. McK., Wislocki, G. B., and O'Leary, J. L.: A précis of preoptic, hypothalamic and hypophyseal terminology with atlas, A. Res. Nerv. & Ment. Dis., Proc. 20:3, 1940.
39. Rowbotham, G. F.: Acute Injuries of the Head, Edinburgh, E. & S. Livingston Ltd., 1949, 480 pp.
40. Scharrer, E., and Scharrer, B.: Secretory cells within the hypothalamus. A. Res. Nerv. & Ment. Dis., Proc. 20:170, 1940.
41. Shimkin, M. B., Boldrey, E. B., Kelly, K. H., Bieman, H. R., Ortega, P., and Naffziger, H. C.: The effects of surgical hypophysectomy in a man with malignant melanoma, J. Clin. Endocrinol. 12:439, 1952.
42. Sinclair-Smith, B. C., Sisson, J., Kattus, A. A., Genecin, A., Monge, C., McKeever, W., and Newman, E. V.: The effects of posterior pituitary extract and smoking on water sodium and chloride excretion in normal subjects and in patients with congestive heart failure, Bull. Johns Hopkins Hosp. 87:221, 1950.
43. Smith, F. M.: Diabetes insipidus: Treatment by intranasal insufflation of posterior lobe pituitary powder, J.A.M.A. 102:660, 1934.
44. Smith, H. W.: The Kidney, New York, Oxford University Press, 1951, 1049 pp.

45. Theobald, G. W.: A Repetition of Certain Experiments in which Molitor and Pick base their Water-Centre Hypothesis and the Effect of Afferent Nerve Stimuli on Water Diuresis, J. Physiol. 81:243, 1934.

46. Theobald, G. W., and Verney, E. B.: The inhibition of water diuresis by afferent nerve stimuli after complete denervation of the kidney, J. Physiol. 83:341, 1935.

47. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. S., and Prichard, M. M. L.: Studies of the Renal Circulation. Springfield, Ill., Charles C Thomas, Publisher, 1947, 187 pp.

48. Van Dyke, H. B.: The regulation of water excretion by the neurohypophysis, Bull. New York Acad. Med. 29:24, 1953.

49. Verney, E. B.: Agents determining and influencing the function of the pars nervosa of the pituitary, Brit. M. J. 2:119, 1948.

50. Vonderahe, A. R.: Changes in the hypothalamus in organic disease, A. Res. Nerv. & Ment. Dis., Proc. 20:689, 1940.

51. Walker, J. M.: The effect of smoking on water diuresis in man, Quart. J. Med, 18:51, 1949.

52. Warkany, J., and Mitchell, A. G.: Diabetes insipidus in children, Am. J. Dis. Child. 57:603, 1939.

■ *Causes of Errors in experimenting upon the Spinal Cord.* Longet declares that it is impossible to lay bare the spinal cord of a mammal without producing, at once, such a debility in the posterior limbs that they lose, more or less completely, both voluntary movements and sensibility. Of course, if mammals were always in this condition after the opening of the spinal canal, it would be quite impossible to perform any valuable experiment on the spinal cord, to find out what are the parts employed in the two functions which are then lost. Fortunately, animals may not have any apparent diminution of either voluntary movements or sensibility after the exposure of the spinal cord to the air. They may walk about and run as fast as if nothing had been done to them, and, except the litte change in the movements of the spine due to the section of some of its muscles, no difference may be observed between them and animals which have not been operated upon. As regards sensibility, it soon becomes increased, as I have stated in a paper read last year to the Royal Society. (See "Proceedings of the Royal Society" 1857, No. 26.) Longet has been mistaken, for the reason, that he opened the spinal canal in a considerable portion of its length, and in so doing produced a state of exhaustion by a great loss of blood and by the excessive pain. When the operation is made quickly, even if a very considerable part of the cord is laid bare, if the hemorrhage has not been great and if pain has been avoided by the exhibition of chloroform, there is no notable diminution of sensibility, and there is no other diminution in the voluntary movements, except that depending upon the section of the muscles of the back.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Sensory Changes in the Upper Limb During Ischemia in Tetany

P. K. Robinson, M.B., M.R.C.P.

TROUSSEAU[1] noted that patients suffering from tetany had a sensation of tingling in the hands and feet, followed by the development of painful cramps of the distal muscles in arms and legs. A chance observation of such a patient during venesection led him to the conclusion that pressure over the nerve trunks or blood vessels of a limb would induce a spasm at will, but it was Lewis[2] who demonstrated experimentally that the spasm was due to ischemia of the nerve trunk under the occluding cuff or clamp.

There has been general agreement between previous investigators of healthy subjects[3,4] on the sequence of events in sensory nerve function following arterial arrest above the elbow; ischemic paresthesias or tingling in the fingers and hand occur first and are followed by gradual sensory loss or numbness which begins in the fingers and spreads centripetally. Kugelberg[5] made certain observations on peripheral nerve function during ischemia in tetany and found that, in this condition, arterial arrest above the elbow is followed by the normal sequence of events (ischemic tingling followed by numbness) but each change begins earlier than in normal subjects.

An opportunity arose to examine two patients suffering from tetany due to spontaneous hypoparathyroidism. Detailed observations were made of the sensory nerve functions during ischemia, particular attention being paid to the onset, extent, and duration of ischemic tingling and numbness, because it was considered that Kugelberg's[5] observations on these points were incomplete. During a relapse of case 1 three years after the first observations, alternative methods of sensory testing were used, enabling a fuller analysis to be made of the early numbness which had been noted during ischemia in the untreated state.

METHODS OF EXAMINATION

Two patients, both suffering from spontaneous parathyroid deficiency, were examined before and after treatment with dihydrotachysterol.

The initial experiments were made under draft-free conditions with room temperatures between 65° and 70° F. (18.3 to 21.1° C.). The patients were examined in the recumbent position, with the pronated arm lying comfortably by their side. A sphygmomanometer cuff (12 cm. wide) was placed just above

From the National Hospital for Nervous Diseases, Queen Square, London.

the antecubital fossa, and after the limb had been held vertically for a few seconds the cuff was quickly inflated to a pressure of 200 mm. Hg. Observations were made on ischemic tingling and the rate of centripetal sensory loss. The sensation of light touch was tested along the axis of the limb, over the extensor surface of the middle finger, the dorsum of the hand, and the extensor surface of the forearm, using a firmly rolled piece of cotton wool lightly placed on the skin in a vertical direction. At regular intervals after arterial arrest the extent of diminished sensibility to cotton wool and the duration of ischemia were observed.

During the relapse of the first case three years later, alternative methods of sensory examination were used. The general conditions were the same. Within a small marked area on the pad of the right middle finger the patient was tested at intervals with a length of standard nylon suture material (equivalent to 0.3 gm.) to determine the number of contacts out of five he was able to detect; this stimulus was easily perceived by the subject in the resting state. In addition, the subjective sensation roused by rubbing the fingers was recorded every minute and the onset of subjective numbness noted.

CASE HISTORIES

Case 1.—A 31 year old man had been subject to generalized and focal seizures since childhood. Since the age of nine years he had suffered from intermittent tetany and laryngeal spasm. Examination revealed a man of short stature with latent tetany, cataracts, dry skin, scant scalp hair, carious teeth, and roentgenographic evidence of calcification in the basal ganglia. Before the first course of treatment the serum calcium level was 5.2 mg. per 100 ml. and the serum phosphorus level 6.2 mg. per 100 ml. Treatment was followed by a good clinical improvement, the serum calcium level rose to 10.8 mg. per 100 ml., and the serum phosphorus level fell to 3.2 mg. per 100 ml. During his relapse the serum calcium level was 7.2 mg. per 100 ml. and the serum phosphorus level had risen to 6.4 mg. per 100 ml. During the second course of treatment, reexamination was carried out at a time when the serum calcium level was 8.2 mg. per 100 ml. and the serum phosphorus level 5.4 per 100 ml.

Case 2.—A 28 year old woman began to have episodic stiffness of her limbs at the age of 18 years. They later became associated with difficulty in breathing. She had no convulsions. On examination latent tetany was present, and radiologic evidence of calcification in the basal ganglia and dentate nucleus was found. Before treatment the serum calcium level was 6.0 mg. per 100 ml. and the serum phosphorus level 5.3 mg. per 100 ml. After treatment the serum calcium level rose to 11.6 mg. per 100 ml. and the serum phosphorus level fell to 2.7 mg. per 100 ml. Both cases have been reported in full (A. N., case 1 and V. H., case 2) by Robinson, Carmichael, and Cumings.[6]

RESULTS

For descriptive purposes the results of the various methods of examination of sensory nerve function during ischemia will be considered under the headings of ischemic paresthesias and numbness.

Ischemic paresthesias. Before treatment, both patients experienced widespread, prolonged, and intense paresthesias during ischemia (figure 1a). The paresthesias did not appear to differ in their essential quality from those experienced by normal subjects and were described as "tingling," although the description was modified by such adjectives as "marked," "severe," "fierce," and on one occasion were likened to "pins and needles." They began in the fingertips within one minute and spread above the elbow in three minutes in case 1 and up to the mid-forearm in seven min-

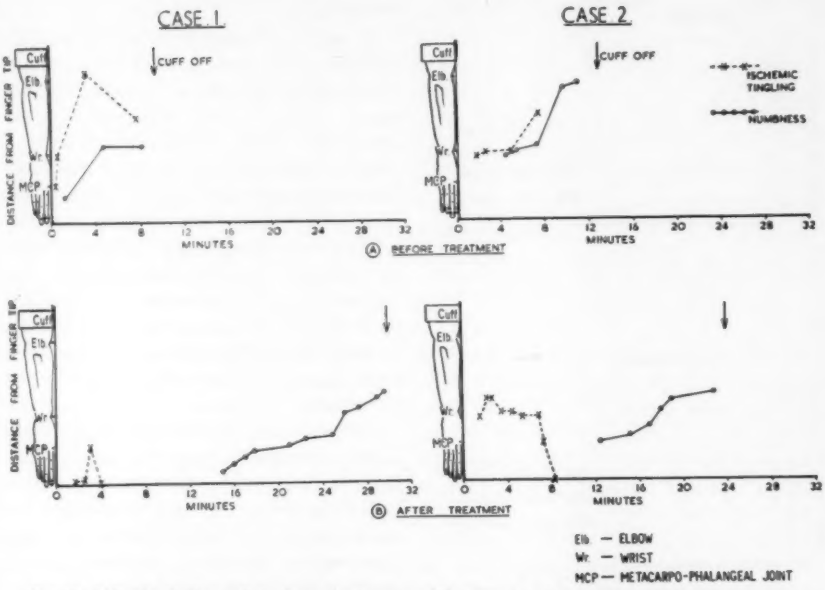


FIG. 1. Ischemic tingling and numbness to cotton wool in cases 1 and 2 (1950). *A*, before treatment; *B*, after treatment. Ordinate: Distance from fingertip up the arm. Abscissa: Duration of ischemia.

utes in case 2 (figure 1a). In both cases tingling was still present after seven and a half to eight minutes, although diminishing in intensity in case 1. After treatment, the ischemic paresthesias were "slight, mild, faint tingling." They began after more than one and a half minutes of ischemia and lasted for two and a fourth and six and a half minutes in cases 1 and 2, respectively. In case 1 they spread to the base of the third and fourth digits, but in case 2 to just above the wrist (figure 1b).

Numbness. Before treatment it was found in both cases that there was an early centripetal impairment of tactile sensation, so that after five minutes of ischemia the appreciation of light touch was impaired up to the wrists in both cases (figure 1a). After treatment, a similar impairment of cutaneous sensation was not found until ischemia had been present in case 1 for 25 to 26 minutes and in case 2 for 17 to 18 minutes (figure 1b).

When the first patient was reexamined during his relapse three years later, the ischemic paresthesias were again early, severe, and widespread and they were rapidly followed by a subjective sensation of numbness in the fingers. The subjective sensations in the fingers were variously described as "numbness" or "like a furry feeling," even after two to four minutes. At this time, however, rubbing produced a normal sensation and it was not until seven and a half minutes that the patient described his fingers as "having a dead feeling," "as if they've been slept on" so that rubbing

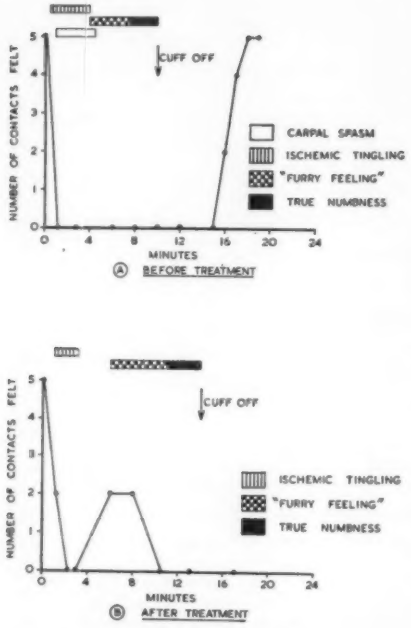


FIG. 2. Sensory testing of case 1 during recent relapse (1953). Groups of fine stimuli with nylon thread every minute. *A*, before treatment; *B*, after treatment. Ordinate: Number of contacts felt. Abscissa: Duration of ischemia.

gave rise to a "really numb feeling" (figure 2a). This was taken as the "time to numbness" referred to by Gilliatt and Wilson.[7]

Following adequate treatment the "time to numbness" increased to 11 minutes. At this stage, appreciation of the contact of a nylon hair was lost after two minutes of ischemia, but was partially restored between four and ten minutes (figure 2b), whereas such contacts had been missed after one minute of ischemia before treatment, without any return of the appreciation of such contacts in a ten-minute period (figure 2a).

DISCUSSION

Kugelberg[5] found that, in the normal subjects, about two minutes after arterial arrest above the elbow, ischemic paresthesias begin in the fingertips, spread up to the wrist, and finally disappear after a lapse of four to eight minutes. These findings agree closely with those of Weddell and Sinclair.[4] In patients with tetany, Kugelberg[5] recorded that the ischemic tingling was earlier in onset and of greater intensity than normal; he recorded its spreading up as far as or even above the elbow, but unfortunately gave no more details of his observations.

The earliest distinct sensory impairment (numbness) over the skin of the fingertips in healthy subjects was found by Lewis, Pickering, and Rothschild[3] to occur 13 to 15 minutes after arterial arrest above the elbow, and the earliest onset of the "velvety numbness" recorded by Weddell and Sinclair[4] was after 15 minutes of ischemia. Kugelberg[5] found that in patients with tetany distal numbness occurred earlier than in healthy subjects. In three patients he recorded anesthesia to cotton wool "up to the middle of the dorsal side of the forearm" after 12, 13, and 15 minutes of ischemia respectively. In a fourth patient there was anesthesia up to the wrist after 16 minutes of ischemia.

It is of interest to note that in testing subjects to determine the extent of early sensory loss in the ischemic limb, both Lewis and co-workers[3] and Weddell and Sinclair[4] used massive tactile stimuli such as stroking, rubbing, or light pressure. Rubbing with the examiner's fingers was found by Gilliatt and Wilson[7] to provide a more constant and easier indication of early sensory change in the fingertips than testing with nylon hairs

in both normal subjects and in patients with peripheral nerve lesions. The duration of ischemia up to the point of changing sensation as determined by rubbing the fingers they called the "time to numbness." In their normal subjects the "time to numbness" for the earliest affected digit was rarely less than ten minutes.

The results of the present study confirm Kugelberg's[5] general observations that in tetany ischemia gives rise firstly to earlier symptoms of excitation and then secondly to earlier loss of function of the sensory nerves than normal, but the present observations provide more detail concerning the rate of development and extent of ischemic paresthesias and sensory loss. The most striking observation was the remarkably early sensory loss during ischemia. In the first set of experiments before treatment, sensory loss to cotton wool appeared when severe, intense paresthesias were present (figure 1a). Testing the first patient with nylon thread during his relapse also showed an early loss of awareness of the stimuli, associated with the ischemic tingling. Gilliatt and Wilson[7] found that by testing normal subjects during ischemia with nylon thread they were able to demonstrate an early deterioration in performance during the period of ischemic tingling. As this latter subsided, awareness of the stimuli improved and did not fall off again until a well-marked subjective change was present. The findings in the above patient with tetany were similar but more marked; after the early deterioration there was no subsequent improvement when testing was done with a stimulus near the threshold (figure 2a); subsequent testing during treatment with graded stimuli, however, showed that the apparent

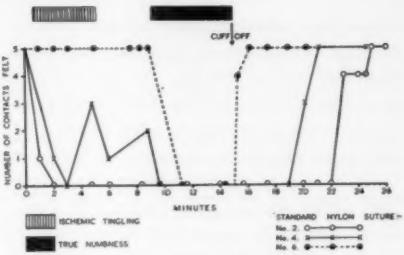


FIG. 3. Sensory testing with graded nylon sutures. Groups of five stimuli with nylon thread every minute. Ordinate: Number of contacts felt. Abscissa: Duration of ischemia.

impairment of sensation was associated with a rise in tactile threshold at the same time as there were symptoms of hyperexcitability (figure 3). Nevertheless, neither of the above methods of sensory testing (cotton wool or nylon thread) made it possible to determine whether the early failure to appreciate the peripheral stimuli during ischemic tingling was due to 1) blocking of the afferent volley arising from the stimulus by spontaneous activity within the nerve, or 2) failure to discriminate centrally between the sensation produced by the stimulus and the spontaneous afferent discharges. The observation in the first experiments that, in case 2, the rate and extent of the sensory impairment was greater although ischemic tingling was less severe and widespread (figure 1a) indicated that there might be a true early numbness from failure of the sensory nerve, in addition to the raised threshold accompanying hyperexcitability.

Examination of the first patient during his relapse three years after the first experiments clarified the findings of the earlier tests. During ischemia in the untreated state his fingers felt numb when stroked seven and a half minutes after arterial arrest above the elbow. Definite

subjective change was present, therefore, at a time when ischemic paresthesias had ceased (figure 2a), and numbness had occurred after a shorter period of ischemia than that needed to produce the same effect in a healthy subject. It was, therefore, reasonable to conclude that in tetany ischemia produced a true early loss of function in sensory nerves. The methods of examination of case 1 used during the recent relapse made it possible to demonstrate this true loss of function and to distinguish it from failure to appreciate a stimulus due to a rise in tactile threshold accompanying hyperexcitability. This distinction had not been possible in the earlier experiments and it is not discussed by Kugelberg.[5]

Clinical observation, therefore, has shown that tetany augments the symptoms of excitation in the peripheral nerves during ischemia and early loss of sensory function follows continued deprivation of oxygen in the presence of a low serum calcium. Experimental evidence has shown that accommodation in frog nerve is reduced,[8] and mammalian nerve shows a reduction in threshold to electrical stimulation and spontaneous discharge[9] under conditions of low calcium concentration. Wigton and Brink[10] and Kugelberg[5] have both found similar reduction in accommodation of peripheral nerves in patients with tetany. Brink, Bronk, and Larrabee[11] have demonstrated in vitro that the oxygen uptake of frog nerve increases when the calcium content of the perfusing fluid is reduced, and although this had not been shown for mammalian nerve, the similarity in the other findings in amphibian and mammalian nerves makes it seem probable that such is the case. The available evidence, therefore, supports Kugelberg's[5] suggestion that in tetany the abnormally early loss of function in the peripheral nerves during ischemia is due, at least in part, to the greater oxygen need entailed by increased activity of the nerve fibers. The syndrome is thus evidence of alteration of function of human peripheral nerves in the presence of a change in the concentration of serum electrolytes.

SUMMARY

1. Sensory peripheral nerve function was examined during ischemia in two cases of hypoparathyroidism and one case was reexamined during a relapse.

2. Kugelberg's general observations on the hyperirritability and early cessation of function of sensory nerves during ischemia in tetany were confirmed, but a fuller analysis was made of the sensory loss.

3. It was shown that there was a true early failure of the sensory nerve, which was not due either to the blocking of the afferent volley arising from the stimulus by spontaneous activity within the nerve, or to the failure to discriminate centrally between the stimulus and the spontaneous afferent discharges.

4. It is suggested that, during ischemia in the presence of a low serum calcium, an initial phase of hyperactivity of the sensory nerves is followed by a premature failure of function.

The author wishes to express thanks to Dr. E. A. Carmichael for his constant encouragement and advice in the completion of this study, and to Dr. G. D. Dawson, Dr. P. W. Nathan, and Dr. R. W. Gilliatt for their helpful criticism.

REFERENCES

1. Trousseau, A.: Clinique Médicale, ed. 3, Paris J. B. Ballière, 1868.
2. Lewis, T.: Trousseau's phenomenon in tetany, Clin. Sc. 4:361, 1942.
3. Lewis, T., Pickering, G. W., and Rothschild, P.: Centripetal paralysis arising out of arrested bloodflow to the limb, including notes on a form of tingling, Heart 16:1, 1931.
4. Weddell, G., and Sinclair, D. C.: "Pins and needles": Observations on some of the sensations aroused in a limb by the application of pressure, J. Neurol., Neurosurg. & Psychiat. 10:26, 1947.
5. Kugelberg, E.: Accommodation in human nerves and its significance for the symptoms in circulatory disturbances and tetany, Acta physiol. Scandinav. 8: Suppl. XXIV, 1944.
6. Robinson, P. K., Carmichael, E. A., and Cummings, J. N.: Idiopathic hypoparathyroidism, a study of three cases, Quart. J. Med. 23:383, 1954.
7. Gilliatt, R. W., and Wilson, T. G.: Ischaemic sensory loss in patients with peripheral nerve lesions, J. Neurol., Neurosurg. & Psychiat. 17:104, 1954.
8. Solandt, D. Y.: The measurement of "accommodation" in nerve, Proc. Roy. Soc., London, s. B. 119:335, 1936.
9. Lehmann, J. E.: The effect of changes in the potassium-calcium balance on the action of mammalian A nerve fibers, Am. J. Physiol. 118:613, 1937.
10. Wigton, R. S., and Brink, F., Jr.: Studies of accommodation of nerve in parathyroid deficiency, J. Clin. Investigation 23:893, 1944.
11. Brink, F., Jr., Bronk, D. W., and Larrabee, M. G.: Chemical excitation of nerve, Ann. New York Acad. Sc. 47:457, 1946.

■ Of the means of experimenting, of which we have already spoken, the one which consists in employing excitations is certainly unable to give any decisive result, as regards the question of the channel by which the sensitive impressions are conveyed to the brain, in the spinal cord. All that may legitimately be deduced from the effects of the excitation of the various parts of the spinal cord is, that a certain part is sensitive, or seems to be, while others seem not to be. Another cause of error exists when we try to find out if a part is sensitive or not. If galvanism is employed, as was the case in the experiments of Longet, it is indeed impossible to have a current applied to the posterior columns, which will not pass by the posterior roots, and as the sensibility of the roots, particularly at the place where they are in connection with the spinal marrow, is excessive, the signs of pain given by the animals do not prove that the posterior columns are sensitive. Experiments in which an irritation is made with the point of a needle or a pin may be considered as insufficient, because the degree of pain, then, is not very great. However, so far as we may draw conclusions from this kind of experiment, it seems very doubtful whether the posterior columns possess any sensibility, and the causes of the mistake which has been made in this respect are, that the posterior roots have been irritated, and that the excitability for reflex action is very great in the posterior columns, and the movements due to the reflex faculty have been considered as signs of pain.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

S. Weir Mitchell on Gunshot Wounds and Other Injuries of Nerves

David J. LaFia, M.D.

HIGH AMONG MEDICAL CLASSICS in any language ranks *Gunshot Wounds and Other Injuries of Nerves,* by S. Weir Mitchell, George R. Morehouse, and William W. Keen published in 1864. It is brief, containing only 164 pages. Not a single illustration complements the text. Its greatness lies in masterful descriptions of nerve injuries simply and thoroughly delineated. We read for perhaps the first time in medical history about causalgia, clearly and vividly described.

The greatness of Mitchell's monograph becomes more apparent when we recall that little of original significance has been added to the clinical study of nerve injuries since 1864, despite the thousands of peripheral nerve injuries in two world wars and Korea.

Mitchell's monograph carves in world medical literature a niche that can best be appreciated when reviewed against the background of medical history during the American Civil War. In the first half of the nineteenth century, France ruled the medical kingdom. She boasted a galaxy of men who forged modern medicine: Xavier Bichat, cofounder with Morgagni of modern pathology; Francois Magendie and Claude Bernard, creators of experimental physiology; Rene Laennec, inventor of the stethoscope; Pierre Louis, founder of medical statistics. Small wonder then that many American physicians flocked to Paris, and S. Weir Mitchell was no exception. About 1850 Germany's medical torch began to glimmer with men like Helmholtz, Virchow, and Ludwig, to mention a few. It burned brilliantly until the twentieth century.

Much of American medicine in the first three-quarters of the nineteenth century was inspired chiefly by European leadership. Yet Americans contributed significantly, foreshadowing an ingenuity that was to make them able world leaders of medicine in the twentieth century. As early as 1825 William Beaumont began his experiments which imaginatively utilized the traumatic gastric fistula of Alexis St. Martin to study the physiology of human digestion. America freed the world from the pain of surgical operations when in 1846 W. T. G. Morton "etherized" a patient at the Massachusetts General Hospital. In 1852 James Marion Sims announced his "epoch-making" operation for vesicovaginal fistula.

From the department of neurosurgery, Jefferson Medical College and Hospital, Philadelphia.

Mitchell's monograph stands preeminently as a paragon of clinical observation. Besides the pioneer description of so-called "burning pain," Mitchell approached nearly every aspect of nerve injuries: sensory impairment, atrophy of muscles, alteration in sweating, and use of physiotherapy and electrical methods in diagnosis and treatment. The pathology of nerve injuries was omitted and for this lack the authors expressed regret.

Modern in viewpoint, Mitchell's volume was ahead of its time. It represents one of the first works of collaboration between neurologists and surgeons, anticipating the special field of neurologic surgery. During the American Civil War patients with nervous disorders were centered at Turner's Lane Hospital in Philadelphia, with Dr. Mitchell in charge. With characteristic energy he seized the opportunity presented to him by an unusual wealth of clinical material on nerve injuries. He brought to this task a well-prepared background, proof that "Chance favors the prepared mind." As a student of Claude Bernard and Francois Magendie in Paris he was aware of their work on vasomotor nerves and the methods of experimental medicine. On his return home around 1850, Mitchell tried to keep up with rapid advances in physiology by writing reviews and doing experiments on snake venom. Later he attracted notice as a neurologist, becoming one of the leaders of his epoch. His skill as novelist, essayist, and poet in no small way must have contributed to the vivid style distinctive of his book.

Mitchell and his colleagues were aware of their unusual opportunity to study peripheral nerve injuries. To quote their first chapter:

"Whatever may be wanting in this essay is, therefore, due alone to its authors, since never before in medical history has there been collected for study and treatment so remarkable a series of nerve injuries." (p. 10)

Two passages sum up the spirit of this work. The first one eloquently expresses the feeling of all those who have worked with such cases:

" . . . . No class of cases with which we have been called to deal seemed to us, at one time, so sadly hopeless as injuries of nerves; none has been rewarded enduring and steady efforts to afford relief. We look back with unfeigned pleasure upon the great number who came to us, despairing cripples, and have left us eased of pain, and either entirely well or so far aided as to enable them to employ their limbs in useful occupations. (p. 157)

" . . . . We shall, therefore, adhere to the rule which has governed us throughout, and only treat fully of points which are novel, or upon which our own clinical experience enables us to cast a clearer light." (p. 101)

These words might well be engraved over the desk of anyone offering an original contribution to medicine.

Practically all types of nerve injuries are mentioned: bullet wounds, sabre cuts, contusion, dislocation, and injuries of the cervical sympathetic trunk and of the fifth and seventh cranial nerves. Mitchell remarks that the study of these injuries was conspicuously absent from the literature of his time.

". . . . Nowhere were these cases described at length in the text-books, and, except in a single untranslated French book, their treatment was passed over in silence; while even in the volume in question but a limited class of nerve lesions were discussed. In the great monographs on military surgery, this defect is still so complete, that wounds of nerves are there related rather as curiosities and as matters for despair, than with any view to their full clinical study and systematic treatment . . . " (p. 10)

His material consisted of about 120 cases with admirably complete notes and as the author says:

" . . . . No labor has been spared in making these clinical histories as perfect and full

as possible. Those only who have devoted themselves to similar studies will be able to appreciate the amount of time and care which we have thus expended . . . . " (p. 12)

Perhaps Mitchell's work on nerve injury lives because of his description of causalgia that has yet to be surpassed in vividness and clarity. He reports relief with blister treatment. Maybe the histamine released from blisters produces a vasodilatation comparable to that obtained from sympathetic nerve blocks? Now for these superb descriptions:

"For these very reasons we have here set apart for distinct consideration that kind of pain which we have before spoken of as burning pain. It is a form of suffering as yet undescribed, and so frequent and terrible as to demand from us the fullest description. In our early experience of nerve wounds, we met with a small number of men who were suffering from a pain which they described as a "burning" or as "mustard red-hot" or as "a red-hot file rasping the skin." In all of these patients, and in many later cases, this pain was an associate of the glossy skin . . . . (p. 101)

"The seat of burning pain is very various; but it never attacks the trunk, rarely the arm or thigh, and not often the forearm or leg. Its favorite site is the foot or hand. In these parts, it is to be found most often where the nutritive skin changes are met with; that is to say on the palm of the hand or palmar face of the fingers, and on the dorsum of the foot: scarcely ever on the sole of the foot or the back of the hand . . . . the great mass of sufferers described this pain as superficial but others said it was also in the joints and deep in the palm . . . . (p. 102)

"The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyper-aesthetic, so that a touch or a tap of the finger increases the pain. Exposure to the air is avoided by the patient with a care which seems absurd, and most of the bad cases keep the hand constantly wet, finding relief in the moisture rather than in the coolness of the application. Two of these sufferers carried a bottle of water and a sponge, and never permitted the part to become dry for a moment.

"As the pain increases, the general sympathy becomes more marked. The temper changes and grows irritable, the face becomes anxious, and has a look of weariness and suffering. The sleep is restless, and the constitutional condition, reacting on the wounded limb, exasperates the hyperaesthetic state, so that the rattling of a newspaper, a breath of air, another's step across the ward, the vibrations caused by a military band, or the shock of the feet in walking, give rise to increase of pain. At last the patient grows hysterical, if we may use the only term which covers the facts. He walks carefully, carries the limb tenderly with the sound hand, is tremulous, nervous, and has all kinds of expedients for lessening his pain. In two cases, at least, the skin of the entire body became hyperaesthetic when dry, and the men found some ease from pouring water into their boots. They said, when questioned, that it made walking hurt less . . . .

"Cold weather usually eased these pains; heat and the hanging down of the limb made them worse . . . . . It appears quite certain that in cases of glossy skin, burning always exists . . . .

"The temperature of the burning part we have always found to be higher than that of surrounding parts, or than that of corresponding points in the other half of the body." (p. 104)

Then Mitchell tries to explain the cause of this burning pain. We today attribute it to derangement in the sympathetic nerve fibers, probably reflexly injured. But Mitchell's explanation is not entirely unlike our own except in terminology. He says:

"The rationale of the production of this form of pain was at first sought for among reflex phenomena. It then seemed to us probable that a traumatic irritation existing in some part of a nerve trunk was simply referred by the mind to the extreme distribution of this nerve, agreeably to the well-known law of the reference of sensations. Further study led us to suspect that the irritation of a nerve, at the point of wound, might give rise to changes in the circulation and nutrition of parts in its distribution, and that these alterations might be themselves of pain-producing nature. The following considerations tend to strengthen the view, that the immediate cause of burning pain lies in the part where the burning is felt. If

the burning were a referred sensation, it would sometimes be met with in cases of complete division of nerves, and, therefore, in parts devoid of tactile sensation. But we have encountered no such cases; and, on the other hand, the burning pain is often accompanied with hyperaesthesia, while motion and touch may remain unaltered. Is it not probable that the depraved nutrition, often so marked in the congested, denuded, and altered skin, may give rise to a disease of the ultimate fibers of the sensitive nerves?" (p. 105)

That this pain could become so intense and intolerable Mitchell illustrates by the following:

"We have again and again been urged by patients to amputate the suffering limb . . . .

"We feel that we may be supposed to have exaggerated somewhat in delineating these hitherto undescribed neural disorders. Surgeons who have happened to encounter a single one of the worst of them, have been so surprised at the character of the suffering as to suspect that such extreme hyperaesthesia must be due, at least in some measure, to a desire on the part of the patient to magnify his pains."

"The pain has consisted all along of darting pangs from below or under the elbow, down into the hand, but not in the anterior surface of the forearm. In the hand, the pain is burning and tingling, or, as he phrases it (referring to the patient who received an injury in the left arm of the ulnar and median nerve), "prinkling." It is intense and is increasing. It is worse in daytime and in hot weather, and when the hand hangs down. Noise and excitement increase it; but it has not reached the state of hyperaesthesia to which it is certainly hastening. The burning lies in the whole of the fingers . . . . but it is worst in the palm . . . . The burning certainly dates back to the moment of the wounding." (p. 108)

From the foregoing quotations we readily see why Mitchell's little volume is a medical classic. His descriptions are not obscured by cumbersome eponyms. Precise observations, not hypotheses, mark his style. He does not quote at every turn the work of others. This makes for original thinking and vigor of form. In Mitchell's work we find what Gordon Holmes had in mind when he said:

"Can we then express in a few words what is required of the clinician who seeks knowledge and truth by the methods of science? In the first place, he must be trained to observe accurately, to see not merely what he is looking for, but to examine all phenomena connected with the question, and to neglect or discard no fact, no matter how apparently trivial. In the second place, he must learn to describe observed facts accurately and completely, but simply and concisely . . . . Too much weight, however, cannot be laid on the importance of avoiding as far as possible in description complicated or technical terms, for these are often a cloak for ignorance or, more seriously, a short cut for shoddy or lazy observations; as in literature, direct expression in the simplest terms is usually the highest ideal. Unfortunately, this warning is not unnecessary to present-day neurology, for a tendency has grown up to employ, often indiscriminately, terms which are insufficiently defined, or which may have to different observers more than one meaning."

Today it seems we have lost this ability, comparing these descriptions of causalgia with those in any standard text of neurology, and the difference is immediately apparent. Truly Osler was right, when advising a young internist, he said, "Let the old men read the new books but you read the old books and the new journals."

REFERENCES

1. Fulton, John F.: Howell's Textbook of Physiology, ed. 15, Philadelphia, W. B. Saunders Company, 1946.
2. Garrison, F. H.: Introduction to the History of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1929.
3. Holmes, Gordon: Neurological Biographies and Addresses, New York, Oxford University Press, 1936.
4. Mitchell, S. W., Morehouse, G. R., and Keen, W. W.: Gunshot Wounds and Other Injuries of Nerves, Philadelphia, J. B. Lippincott Company, 1864.

The Hypothalamic Syndrome in Rats with Experimental Lesions

Leo C. Massopust, Jr., Ph.D.

As LONG AGO as 1921 is was suspected that adiposity could result from dysfunction of the hypothalamus. Bailey and Bremer[1,2] produced a "questionable" obesity in some dogs by puncturing the hypothalamus at points distributed from the infundibular stalk to the anterior border of the mammillary bodies. Lesions have since been placed by various methods in almost every area of the hypothalamus in a number of species of laboratory animal by investigators studying the problem of hypothalamic obesity.

The area of the hypothalamus which must be intact to prevent abnormal deposition of fat has been stated to be the anterior area including the area around the paraventricular nuclei[3,4] the region in and around the ventromedial nuclei,[5,6] and the region caudal to the tuberal area impinging upon the mammillary area.[7,8] The evidence presented by Hetherington and Ranson,[5–8] Anand and Brobeck,[9] Greer,[10] Delgado and Anand,[6] and Barnett and Mayer[11] leaves little doubt that the essential area is the region of the ventromedial nuclei of the hypothalamus.

While our primary interest in this study was the phenomenon of obesity, other physiologic abnormalities were observed, including sham rage, disturbances in estrus cycles, and disturbances in body temperature.

A number of factors and circumstances have been described which may contribute to the abnormal deposition of lipoids in animals with hypothalamic lesions. Hyperphagia, voracity, and polydipsia seem to play important roles in this phenomenon, according to Brooks, Lockwood, and Wiggins,[12] Hetherington and Weil,[13] Stominger,[14] and Kennedy.[15] A breakdown of the balance between food intake and energy utilization contributes to the development of obesity in animals with hypothalamic lesions.[7,16,17] Hetherington and Weil,[13] Hetherington and Ranson,[18–20] Heinbecker, White, and Rolf,[3] and Lundbaek and Stevenson[21]

From the department of anatomy, University of Colorado School of Medicine, Denver.
This investigation was supported in part by a research grant (PHS A-206-R) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and in part by a grant from the Office of Naval Research.
Author's present address: Laboratory of Neuroanatomical Sciences, National Institutes of Health, Bethesda, Maryland.

have attributed adiposity in animals with hypothalamic lesions to abnormalities in carbohydrate and fat metabolism. A disturbance in the relationship between food intake and activity in animals with lesions of the ventromedial nuclei may also be a factor contributing to the obese condition.[18–20]

Many methods have been used to produce lesions in the hypothalami of experimental animals. The most common methods have been surgical removal of part of or the whole of the hypothalamus, needle punctures in various regions of the tuber cinereum, and electrolytic lesions of specific areas by means of various types of stereotaxic instruments. The use of the stereotaxic instrument has produced the most consistently bilaterally symmetrical lesions. In this work the stereotaxic instrument devised by Sherwood, Massopust, McCrum, and Buchanan[22] was used to produce, by a single insertion of the electrode, bilateral lesions perpendicular to the midsagittal plane of the brain, thus minimizing the amount of brain tissue traversed by the electrode to reach the hypothalamus and permitting more precise control of the lesion's size and limits.

METHODS

Lesions were placed in various areas of the hypothalami of 85 Sprague-Dawley rats of both sexes by means of electrolysis. The experimental procedure was essentially the same as that described previously.[22] The time of application of current to the indwelling electrode was 13 seconds.

The operated animals were placed in individual cages in an air-conditioned temperature-regulated room which was maintained at 27° C. All rats, both experimental and control, were fed *ad libitum* rat pellets, fresh lettuce, and water. The rats were weighed daily for the first two weeks after the operation, then weekly for three weeks and finally monthly for two to four months.

Thirty-four of these operated rats were used in body temperature and metabolism studies which have been published in this journal.[25] Twelve rats died within a few hours after the operation from hemorrhage. Twenty-four died from inanition which will be discussed further in the results of this experiment. Fifteen remaining rats (six males and nine females) with hypothalamic lesions were selected from 85 operated rats for this study on the basis of their rapid weight gain.

Estrus cycles were studied on six obese female rats. Vaginal smears were then taken daily for two weeks on these six animals when it became apparent they were becoming fat (about five weeks after operation).

Colonic temperatures were taken routinely on all animals by means of a centigrade rectal thermometer. The bulb of the thermometer was inserted about two inches through the anus.

At the end of two of four months following the operation, rats were sacrificed and autopsies performed. The brains of the operated rats were fixed in 10 per cent formalin for two days before the hypothalamus was removed, dehydrated, and imbedded in paraffin. Frontal sections (15 micra) were made from each imbedded hypothalamus; odd numbered sections were stained for myelin by the method of Weil,[23] and even numbered sections for cell bodies by the method of Tress and Tress.[24]

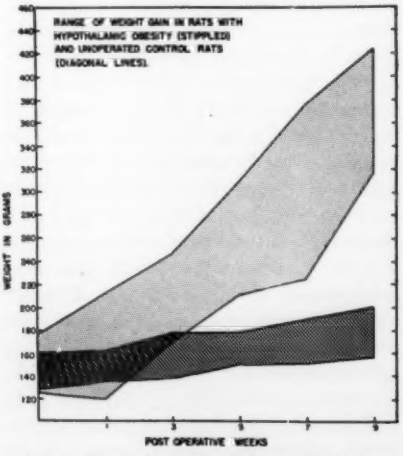

RANGE OF WEIGHT GAIN IN RATS WITH HYPOTHALAMIC OBESITY (STIPPLED) AND UNOPERATED CONTROL RATS (DIAGONAL LINES).
WEIGHT IN GRAMS
POST OPERATIVE WEEKS

FIG. 1. Range of weight gain in unoperated control rats and rats with hypothalamic lesions.

TABLE 1

MAGNITUDE OF DESTRUCTION OF NUCLEI AND AREAS OF THE HYPOTHALAMUS BY LESIONS IN INDIVIDUAL ANIMALS

Rat No.	*Sex*	*Estrus cycles*	*S.O.*	*S.C.*	*S.D.*	*A.A.*	*P.E.*	*A.*	*V.M.N.*	*L.A.*	*F.*	*D.M.N.*	*M.E.*	*P.A.*	*S.M.A.*	*M.M.*	*F.F.*
1014	F	•	xxx	xxx	xxx	xx	x	xx	x	x							
1064	F	•	xx	xxx	xxx	xxx	xx	xx	xx	xx	x						
1002	F	o	xx	xx	xx	xxx	x	x	xx	xx							
1012	F	•	xx	xx	xx	xx	xx	xx	xx	xx							
1068	F	•			x	xx	xx	xxx	xx								
1004	M					x	x	xx	xxx	xx	x						
1070	F	+				x	xx	x	xxx	xx							
1022	M						x	xx	xxx	xxx							
982	M						x	x	xx	xx							
992	M							xx	xxx	xx							
960	F	o					x	x	xx	xx	xxx						
680	F	o					xx	x	xxx	xx	xxx						
986	M						xx	xx	xxx	xx	xxx	x					
1018	M							xxx	xxx	xx			xx				
1066	F	•							xx	xx			xxx				

Abbreviations as follows: *A.*—Arcuate hypothalamic nuclei; *A.A.*—Anterior area of the hypothalamus; *D.M.N.*—Dorsomedial hypothalamic nuclei; *F.*—Fornix; *F.F.*—Fields of Forel; *L.A.*—Lateral area of the hypothalamus; *M.E.*—Median eminence; *M.M.*—Medial mammillary nuclei; *P.E.*—Periventricular system; *P.A.*—Posterior hypothalamic area; *S.C.*—Suprachiasmatic nuclei; *S.D.*—Diffuse supraoptic nuclei; *S.O.*—Supraoptic nuclei; *S.M.A.*—Supramammillary area; *V.M.N.*—Ventromedial hypothalamic nuclei.

x Slight damage
xx Moderate damage
xxx Severe damage
• Remained in estrus
o No estrus cycles taken
+ Fluctuated between preestrus and estrus

RESULTS

Although actual quantities of food and water intake were not determined for the animals displaying obesity, it was observed that large amounts of food and water were consumed. The ranges of weight gain in the 15 obese animals as compared to the controls are shown in figure 1. Twenty-four animals with lesions in the tuberal area of the hypothalamus refused to eat and rapidly lost weight; a loss of 50 to 60 gm. was fatal, usually within seven days. Further studies must be made on these starvation animals to determine the precise location and characteristics of lesions responsible for this loss of weight.

Colonic temperatures of the obese rats were within the normal range (36 to 38° C.). Those of starvation animals were generally much lower than the normal range (34 to 28° C.).

Examination of the frontal serial sections of the hypothalami of the 15 obese rats revealed that the lesions were either filiform, umbonate, spindle-shaped, or cylindrical. Thirteen of the lesions were located in tuberal areas of the hypothalami; two of these impinged upon the anterior area. Table 1 indicates the relative damage to the various nuclei and areas of the hypothalamus produced by the lesions in each of the obese rats. Generally, moderate or large sized lesions caused the greatest degree of adiposity and the most rapid weight gain. It appears that in the case of anterior or ventral tuberal lesions only extensive destruction produces a considerable degree of adiposity, while lesions imping-

ing upon the lateral areas and the areas in and around the ventromedial nuclei need not be large. Several small mid-tuberal lesions producing various degrees of obesity were found to be discrete and almost thread-like.

All 15 of the obese rats which were carefully followed displayed sham rage, characterized by increased irritability and exaggerated responses to external stimuli. As obesity progressed, sham rage regressed, though still evident to a minor extent about four months following the operation.

It was found that disturbances in estrus cycles of these obese rats appeared when lesions were located in one of three distinct areas. Of the six female rats studied, five remained in estrus during the two-week test period. Four of these had lesions which involved bilaterally the area of the supraoptic and suprachiasmatic nuclei, the area of the diffuse supraoptic nucleus, and the anterior area of the hypothalamus. A fifth rat showed a lesion located in the median eminence and the ventromedial nuclei. The remaining obese female rat with a lesion located in the tuberal area of the hypothalamus fluctuated between pre-estrus and estrus (table 1).

The appearance of a large number of epithelial cells in the vaginal smear was taken to indicate pre-estrus, and cornified epithelial cells, estrus.

DISCUSSION

It was obvious on observing the eating habits of the obese rats that they were hyperphagic and polydipsic. Certainly these phenomena contributed to the development of adiposity when lesions were appropriately placed bilaterally in the hypothalamus.[29] The relationship of activity of these animals to the obese condition was not evaluated. Since the individual cages in which the animals were kept were small, it is possible that the curtailment of activity contributed minimally to the development of obesity in these animals.

The most extensive lesions were in those four obese rats (table 1, rats 1002, 1012, 1014, 1064) that had bilateral damage which extended from the region just above the optic chiasm to the midpoint of the median eminence. This is in agreement with reports[3,4,10] that obesity results from so-called anterior hypothalamic lesions. It appears that lesions of the anterior hypothalamus must be extensive in order to produce adiposity. It is probable that these anterior lesions were extensive enough to impinge upon the ventromedial nuceli and the lateral areas of the hypothalamus. Small or thread-like lesions of the anterior hypothalamus, however, failed to produce the adipose condition.

There were four obese rats (rats 960, 982, 992, 1022) with filiform or cylindrical lesions, three of which showed lesions of moderate size confined largely to the ventromedial nuclei, the lateral areas, and the periventricular system. The fourth animal had a thread-like lesion, similarly placed, which seemed to occupy about one-fifth of the area of the lesions in any of the other three rats. From this it is postulated that the lesions in this region need not be large to result in obesity, provided that both the ventromedial nuclei and the areas immediately lateral to the ventromedial nuclei are damaged or destroyed. Since some of our operated rats died of starvation with similarly placed lesions it is probable that a "feeding center" as proposed by Anand and Brobeck[9] and Delgado and Anand[6] lies either in the extreme

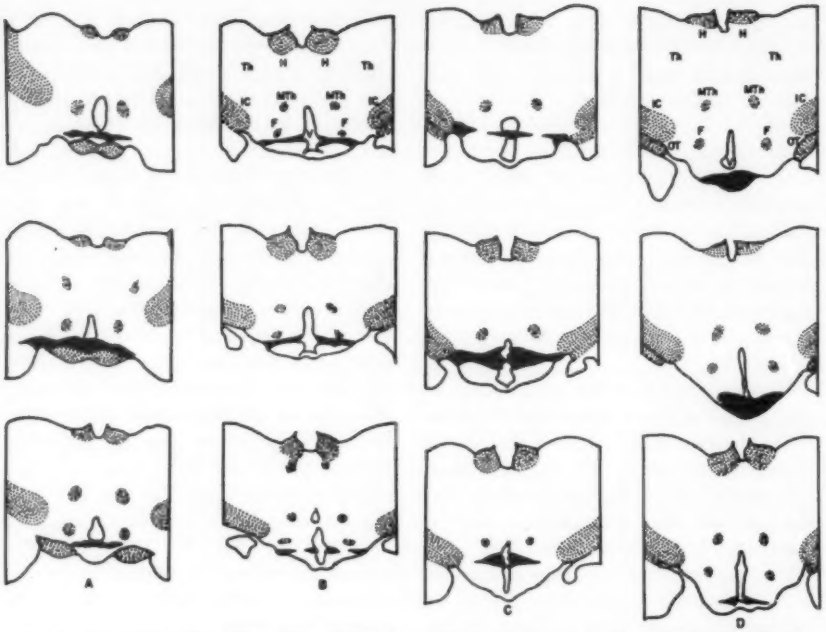


FIG. 2. Three representative sections each through the brainstems of rats with hypothalamic lesions, illustrating the most anterior lesion (A) and the most posterior lesions (B) producing obesity.

FIG. 3. Three representative sections each through the brainstems of rats with hypothalamic lesions, illustrating the most dorsal lesion (C) and the most ventral lesion (D) producing obesity.

posterolateral part of the lateral area of the hypothalamus or dorsolateral to the ventromedial nuclei.

Ventrotuberal or midtuberal hypothalamic lesions do not cause disturbances in temperature regulation; this is in conformity with an earlier report by Massopust and associates.[25] The low colonic temperatures found in the starvation animals could be caused either by inanition or by a dysfunction of temperature regulating mechanisms.[22,25]

The area whose dysfunction causes hypothalamic obesity in the rat is bounded by the supraoptic area anteriorly, the ventromedial nuceli dorsally, the median eminence both ventrally and caudally, and the internal capsule laterally (figure 4). Figures 2 and 3 illustrate the animals with the most anterior lesion, the most posterior lesion, and the most dorsal and most ventral lesions. Damage or destruction of all or part of this area causes an abnormally rapid gain of weight and the deposit of large amounts of lipoid material in the mesenteries, around the internal organs of the abdominal cavity, and in the subdermal layers.

Sham rage exhibited by all of the obese animals presumably reflects either a "release" of hypothalamic inhibition on the cortex or the loss of control by the cortex over the hypothalamus.[26–28] Lesions unintentionally placed in the thalamus in preliminary experiments did not result in the appearance of rage.

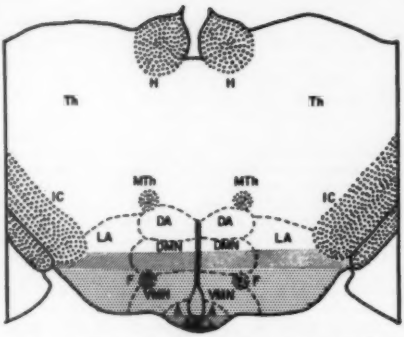


FIG. 4. Composite diagram showing the area which if destroyed (stippled) and damaged (diagonal lines) causes obesity and sham rage. Abbreviations used in illustrations as follows: A, arcuate hypothalamic nucleus; DA, dorsal area of hypothalamus; DMN, dorsomedial hypothalamic nuclei; F, fornix; H, habenula; IC, internal capsule; LA, lateral area of the hypothalamus; ME, median eminence; MTH, mammillothalamic tract; Th, thalamus; VMN, ventromedial nuclei of the hypothalamus.

Damage or destruction of the supraoptic area and the postchiasmatic area of the hypothalamus upsets the normal estrus cycle. According to Greer,[10] animals exhibiting persistent estrus had lesions ventral to and slightly rostral or caudal to the paraventricular nuclei. In our study, four out of five obese female rats, which showed constant estrus for the two-week period during which vaginal smears were taken, had lesions restricted to the suprachiasmatic and postchiasmatic areas. These lesions, however, never reached far enough dorsally to involve either the paraventricular nuclei or the areas immediately surrounding these nuclei. The fifth rat of the obese females which remained in constant estrus had a lesion which involved principally the area of the median eminence. On the basis of the diverse lesion sites which produced constant estrus, it is postulated that the significant area includes the supraoptic nuclei, the suprachiasmatic nuclei, the diffuse suprachiasmatic nucleus, and the anterior area of the hypothalamus (rats 1014, 1064, 1012, 1068). The posterior extension of this area might in some cases involve the hypothalamico-hypophyseal tract (rat 1066).

Our data are inadequate to explain the case of one obese female rat in which the lesion was found to be principally in the ventrolmedial nuclei, the lateral areas, and the periventricular system and whose estrus cycle fluctuated between pre-estrus and estrus (rat 1070).

SUMMARY

Lesions were placed in the hypothalami of Sprague-Dawley rats by means of electrodes inserted perpendicular to the midsagittal plane of the brain. Some with low colonic temperatures died of starvation. Others (15 rats) exhibited hyperphagia, polydipsia, obesity, and sham rage; none of these showed changes in colonic temperatures. The female rats in which the estrus cycles were studied showed disturbances of the cycle.

The lesions responsible for obesity were bilaterally symmetrical, either filiform, umbonate, spindle-shaped, or cylindrical, sometimes bridging the third ventricle, in the anterior portion of the ventrotuberal hypothalamus. Large and extensive lesions of the anterior hypothalamus were usually necessary to produce the obese condition or changes in estrus cycles; small lesions in this area failed to produce these conditions. Midtuberal lesions of the hypothalamus need not be large. It was found that threadlike lesions, provided they damage part of the ventromedial nuclei and the areas immediately lateral to these nuclei, were sufficient to produce the obese condition without changes in estrus cycles or colonic temperatures.

REFERENCES

1. Bailey, P., and Bremer, F.: Experimental diabetes insipidus and genital atrophy, Endocrinology 5:761, 1921 (a).
2. Bailey, P., and Bremer, F.: Experimental diabetes insipidus, Arch. Int. Med. 28:773, 1921 (b).
3. Heinbecker, P., White, H. L., and Rolf, D.: Experimental obesity in the dog, Am. J. Physiol. 141:549, 1944.
4. Mayer, J., Bates, M. W., and Van Itallie, T. B.: Blood sugar and food intake in rats with lesions in the anterior hypothalamus, Metabolism 1:340, 1952.
5. Hetherington, A. W., and Ranson, S. W.: Hypothalamic lesions and adiposity in the rat, Anat. Rec. 78:149, 1940.
6. Delgado, J. M. R., and Anand, B. K.: Increase of food intake induced by electrical stimulation of the lateral hypothalamus, Am. J. Physiol. 172:162, 1953.
7. Brooks, C. Mc., and Lambert, E. F.: A study of the effect of limitation of food intake and the method of feeding on the rate of weight gain during hypothalamic obesity in the albino rat, Am. J. Physiol. 147:695, 1946.
8. Brooks, C. Mc., Marine, D. N., and Lambert, E. F.: A study of the food-feces ratio and of oxygen consumption of albino rats during various phases of experimentally produced obesity, Am. J. Physiol. 147:717, 1946.
9. Anand, B. K., and Brobeck, J. R.: Hypothalamic control of food intake, Yale J. Biol. & Med. 24: 123, 1951.
10. Greer, M. A.: The effect of progesterone on persistent vaginal estrus produced by hypothalamic lesions in the rat, Endocrinology 53:380, 1953.
11. Barnett, R. J., and Meyer, J.: Endocrine effects of hypothalamic lesions, Anat. Rec. 118:374, 1954.
12. Brooks, C. Mc., Lockwood, R. A., and Wiggins, M. L.: A study of the effect of hypothalamic lesions on the eating habits of the albino rat, Am. J. Physiol. 147:735, 1946.
13. Hetherington, A. W., and Weil, A.: The lipoid, calcium, phosphorus and iron content of rats with hypothalamic and hypophyseal damage, Endocrinology 26:723, 1940.
14. Stominger, J. L.: The relation between water intake and food intake in normal rats and in rats with hypothalamic hyperphagia, Yale J. Biol. & Med. 19:279, 1947.
15. Kennedy, G. C.: The hypothalamic control of food intake in rats, Proc. Roy. Soc., London, s. B. 137:535, 1950.
16. Brobeck, J. R., Tepperman, J., and Long, C. N. H.: Experimental hypothalamic hyperphagia in the albino rat, Yale J. Biol. & Med. 15:831,1942.
17. Brooks, C. Mc.: The relative importance of changes in activity in the development of experimentally produced obesity in the rat, Am. J. Physiol. 147:708, 1946.
18. Hetherington, A. W., and Ranson, S. W.: The spontaneous activity and food intake of rats with hypothalamic lesions, Am. J. Physiol. 136:609, 1942.
19. Hetherington, A. W., and Ranson, S. W.: The relation of various hypothalamic lesions to adiposity in the rat, J. Comp. Neurol. 76:475, 1942.
20. Hetherington, A. W., and Ranson, S. W.: Effect of early hypophysectomy on hypothalamic obesity, Endocrinology 31:30, 1942.
21. Lundbaek, K., and Stevenson, J. A. F.: Reduced carbohydrate intake after fat feeding in normal rats with hypothalamic hyperphagia, Am. J. Physiol. 151:530, 1947.
22. Sherwood, C., Massopust, L. C. Jr., McCrum, W. R., and Buchanan, A. R.: The effect of hypothalamic lesions upon body temperature maintenance in the albino rat while in cold environments, J. Neuropath. & Exper. Neurol. 13:191, 1954.
23. Weil, A.: A rapid method of staining myelin sheaths, Arch. Neurol. & Psychiat. 20:392, 1928.
24. Tress, G., and Tress, M.: A modification of the cresyl-violet technique for staining nerve cells, Stain Technol. 10:105, 1935.
25. Massopust, L. C., Jr., Sherwood, C., McCrum, W. R., and Buchanan, A. R.: Metabolic reactions to cold stress of rats with hypothalamic lesions, Neurology 4:283, 1954.
26. Bard, P.: A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system, Am. J. Physiol. 84:490, 1928.
27. Wheatley, M. D.: The hypothalamus and affective behavior in cats, Arch. Neurol. & Psychiat. 52:296, 1944.
28. Waife, S. O.: The pathogenesis of obesity, Am. Pract. 2:47, 1947.
29. Brobeck, J. R.: Mechanism of the development of obesity in animals with hypothalamic lesions, Physiol. Rev. 26:541, 1946.

Ballism Associated with Partial Destruction of the Subthalamic Nucleus of Luys

Malcolm B. Carpenter, M.D.*

NEUROLOGIC INTEREST and curiosity concerning human ballism seems out of proportion to the reported incidence of this relatively uncommon form of dyskinesia, as evidenced by the fact that several rather complete reviews of the subject have been made [1–5] since ballism, as an entity, became associated with pathologic changes in the subthalamic nucleus of Luys. This interest may stem in part from the fact that the syndrome is rare or that the etiology and pathogenesis of ballism appears readily understandable in comparison with other types of dyskinesias associated with widespread pathology of the extrapyramidal system.

Opportunity to study cases of ballism clinically and pathologically are infrequent; Whittier found reports of only 60 cases in the literature, of which only 30 were sufficiently complete and accurate to warrant analysis. Since this review was written a few additional cases have been published.[5–10] Six authors[1,8,9,11–16] have described two cases of ballism clinically and pathologically; Bertrand[8,16,17] reported three cases during a period of 16 years. Cases of ballism which at autopsy have been associated with isolated lesions of the subthalamic nucleus without antecedent or coexisting neural lesions elsewhere are infrequent; only 14 such cases were found in the literature by Carpenter and Carpenter.[18] In spite of the fact that many brains with localized lesions (mostly vascular necrotizing in type) involving the subthalamic nucleus have been examined pathologically, information concerning the fiber connections of this important structure is still incomplete. Human material studied for fiber degeneration by the Marchi method is unusual. Although experimental studies of the subthalamic nucleus[19–24] in carnivora and primates have recently yielded considerable physiologic data, information concerning the intricate afferent and efferent fiber connections is still deficient.

Apparent relationships between the sites of dyskinesia (choreoid and ballistic) associated with complete and partial destruction of the subthalamic nucleus have led various investigators[11,13,25] to postulate an intranuclear somatotopic schema for the human corpus Luysi. A study[18] of clinicopathologic case reports in the literature revealed only 14 cases with partial lesions of the sub-

From the department of anatomy, Columbia University College of Physicians and Surgeons, New York City.

*John and Mary R. Markle scholar in medical science.

This work aided by grants (B386 and B387) from the Department of Health, Education and Welfare, administered by Dr. Fred A. Mettler, department of neurology.

thalamic nucleus; these were described in varying degrees of detail which made comparisons difficult and probably inaccurate. Data were tabulated in such a manner as to weigh both positive and negative evidence for the thesis that destruction of the oral pole of the nucleus may be associated with dyskinesia involving the facial, glossal, cervical, and deglutitional musculature. These data were inconclusive. On the basis of clinical findings it is practically impossible to distinguish between cases of complete and partial destruction of the subthalamic nucleus.

The present case, in spite of its incompleteness, seemed of importance since it afforded an opportunity to study by the Marchi method degeneration resulting from a 23 day old lesion and to explore the question of somatotopic localization within the nucleus. Only a brief clinical summary will be given, since the clinical aspects of this case are to be reported elsewhere.

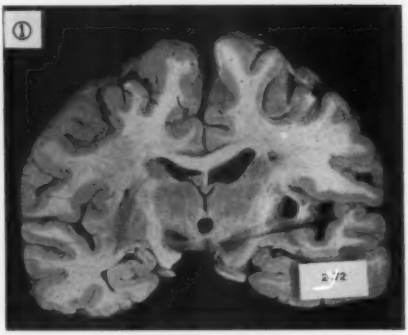


FIG. 1. Photograph of gross brain section showing old (six years) cystic lesion in the left putamen and a recent (23 day old) lesion in the right subthalamic nucleus.

CASE REPORT

A 73 year old man who had suffered from hypertension for at least 12 years sustained a cerebrovascular accident six years prior to admission which resulted in a right hemiparesis with agraphia. The hemiparesis diminished in time but a residual agraphia remained. On February 26, 1953 the patient apparently slipped and fell, striking the occipital portion of the skull. Although stunned, he was said not to have lost consciousness. Immediately after the fall the patient developed abnormal involuntary jerky movements in his left extremities which persisted and increased in frequency and violence. Twenty-four hours after the fall the activity was described as being typical of ballism and of such a forceful nature as to "completely throw him out of bed." Activity was slightly more marked in the upper extremity than in the lower, though the difference was small. Slight abnormal activity was present in the cervical musculature, but no abnormal involuntary activity was noted in the facial, glossal, or deglutitional musculature. Neurologic examination on admission revealed only mild hypesthesia and diminished proprioceptive and vibratory sense in the left extremities in addition to the ballistic activity. Large amounts of Demerol and various barbiturates did not seem to ameliorate or reduce the dyskinesia, except to induce sleep; during sleep all abnormal involuntary activity ceased. On March 11, 1953 a ventriculogram was performed which was within normal limits. Because of progressive deterioration in the patient's general condition, a left ventrolateral cordotomy was performed at the level of the third cervical segment under local anesthesia. Postoperatively the ballistic activity was said to have been controlled and no clinical evidence of a pyramidal deficit could be detected. The patient developed a confluent bronchopneumonia and died on March 21, 1953 despite chemotherapy and postural drainage.

Pathologic findings: At autopsy the brain and portions of the first and second cervical segments of the spinal cord were removed. Grossly the brain appeared normal in size, shape, and appearance, except for moderately severe arteriosclerosis of the large vessels at the base. Gross sections of the brain revealed an old cystic cavity in the left putamen (six years old) which measured 6 x 6 mm. in maximal dimensions and a recent hemorrhagic lesion in the right subthalamic nucleus. On section the subthalamic lesion appeared to extend from the lateral to the medial pole of the nucleus. The remainder of the neuraxis examined appeared grossly normal.

Microscopic study: Blocks of tissue including portions of the basal ganglia and thalamus and serial blocks of the brainstem were cut approximately 2 to 3 mm. in thickness, impregnated according to the method of Marchi, embedded in celloidin, and sectioned at 23 μ. Every tenth section was mounted. Sections of the cerebellum were embedded in paraffin and stained with cresyl violet.

FIG. 2. Recent hemorrhagic lesion in the internal capsule immediately rostral to subthalamic nucleus.

FIG. 3 and 4. Photomicrographs of lesion in the right subthalamic nucleus at different levels.

Diencephalon: On the right side a recent small vascular lesion was located dorsal to the optic tract at the junction of the apex of the internal segment of the globus pallidus and the internal capsule; portions of both structures were destroyed, though destruction was greatest in the internal capsule. Fine scattered Marchi degeneration surrounded the lesion. Some of the fibers of the internal capsule appeared degenerated, but the most heavily degenerated fibers traversed the internal capsule and passed toward the hypothalamus and thalamus. The ventral division of the ansa lenticularis contained heavily degenerated fibers. In sections through the rostral pole of the subthalamic nucleus a triangular shaped vascular lesion occupied the lateral third of the nucleus, bounded dorsally by the dorsal division of the ansa lenticularis and laterally by the internal capsule. These bordering fiber structures contained some degeneration. In more caudal sections the vascular lesion spread medially within

the subthalamic nucleus, remaining in its dorsal half and assuming a linear configuration oriented in the long axis of the nucleus. This linear lesion extended almost the entire width of the nucleus at some levels. The central portion of the lesion contained cellular debris, blood cells, and blood pigments. Marchi degeneration in the dorsal division of the ansa lenticularis and the subthalamic fasciculus could be traced through the internal capsule and into the globus pallidus (retrograde degeneration). Little, if any, degeneration was seen in the thalamic fasciculus or in the zona incerta. Sections through the thalamus appeared normal. The rostral portions of the substantia nigra contained scattered Marchi degeneration, but the melanin pigments appeared normal in amount and distribution. The rostral portions of the red nucleus were normal.

A small cystic lesion of relatively recent origin surrounded by Marchi granules was found in the dorsolateral portion of the right putamen at its junction with the pallidum. It measured 0.75 x 1.67 mm. in maximal dimensions (ocular micrometer). Degenerated fibers emanating from the vicinity of this lesion passed into the lateral segment of the globus pallidus.

On the left an old cystic cavity measuring 6 x 6 mm. in maximal dimensions was found in the dorsolateral portion of the putamen. No Marchi granules surrounded its borders. The striations of the putamen in its vicinity were pale and less distinct than in the ventral part of the putamen. The thalamus, globus pallidus, internal capsule, subthalamic nucleus, substantia nigra, and red nucleus appeared normal.

Brainstem: Microscopic sections of the mesencephalon appeared normal. No Marchi degeneration was noted in the brachium conjunctivum. In the upper pons several small vascular lesions of old and recent origin were found, mostly near the midline. An old softening (approximately 2 x 0.6 mm.) was located on the right side in the dorsal transverse pontine fibers and extended laterally to involve the medial portion of the medial lemniscus. Other minute lesions of recent origin were situated near the midline dorsal to the corticospinal tracts. Some of the blood vessels surrounding these lesions appeared dilated and engorged. A small medial portion of the medial lemniscus was distinctly degenerated in the pons, but this degeneration could not be followed for any distance in either direction.

Sections through the medulla were within normal limits, except for questionable degeneration in the region of the ventral arcuate nuclei on the right. The medial lemniscus, inferior olivary nuclei, and the pyramids appeared normal.

Spinal cord: A wedge-shaped area of degeneration was found in the lateral funiculus of the spinal cord at the level of the first cervical segment, ventral to the descending spinal tract of the trigeminal and occupying the area of the dorsal and ventral spinocerebellar tracts and part of the area through which the corticospinal and rubrospinal tracts pass. Scattered coarse degeneration was present bilaterally in the fasciculi cuneati. The rostrocaudal extent of these degenerations was small and at the second cervical level only a small vascular lesion was present near the central grey, together with the scattered degeneration in the fasciculi cuneati.

Sections of the spinal cord below this level and in the operative area were, unfortunately, not available for study, since most of the spinal cord was not removed at autopsy.

Summary of pathologic findings: Grossly the brain and upper two cervical segments of the spinal cord appeared normal, except for moderately severe arteriosclerosis of the large vessels at the base of the brain. On sectioning the brain an old (six years) cystic cavity (6 x 6 mm.) was found in the dorsal portion of the left putamen. A recent (23 days old) vascular lesion was present in the right subthalamic nucleus. Microscopic study of Marchi-stained sections of the brain revealed a small vascular lesion involving the internal capsule and globus pallidus immediately rostral to the subthalamic nucleus, which appeared to be contiguous with the lesion in that structure. The lesion of the subthalamic nucleus was partial, destroying the lateral third of the nucleus rostrally and the dorsal third in more caudal sections. A planimetric profile of the subthalamic nucleus[26] revealed that the lesion extended throughout the length of the nucleus and destroyed approximately one third (31 per cent) of its volume. The volume of the right subthalamic nucleus was estimated to be 101 cu. mm.; the left was found to be 118 cu. mm. Approximately 31 per cent of the right subthalamic nucleus was destroyed. Marchi degeneration was present in the dorsal, middle, and ventral divisions of the ansa lenticularis[27] on the right side, as well as in the rostral portion of the substantia nigra. In the mesencephalon and pons several small, old and recent, vascular lesions were found, mostly near the midline. In the upper cervical segments of the spinal cord a wedge-shaped area of degeneration was found on the left in the lateral funiculus (parasurgical extension of the operative lesion).

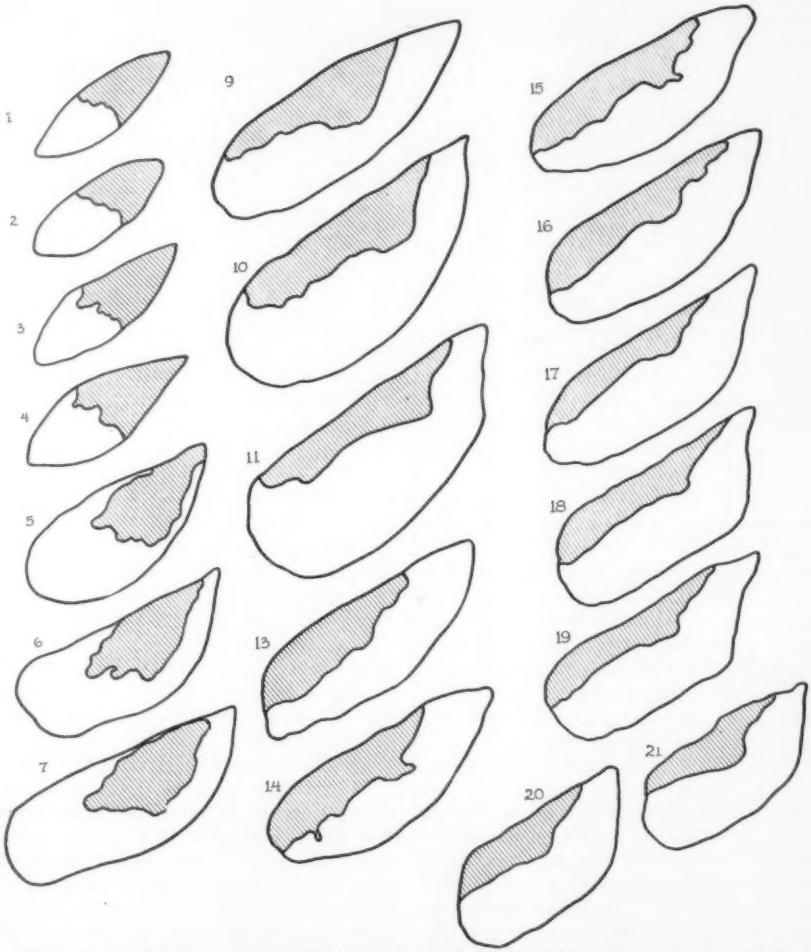


FIG. 5. Outline drawings of the subthalamic nucleus and the lesion within the nucleus at various levels between the rostral and caudal poles of the nucleus, the first being rostral and the twenty-first caudal.

DISCUSSION

A significant predilection for ballism to occur in the left extremities was found in a review of 41 cases reported in the literature (table 1). In 63 per cent of these cases the left extremities were involved (left side, 26 cases; right side, 15 cases). No reason for this laterality could be determined, except in the case described by Martin[1] in which a vascular anomaly was found. In this particular case the basilar artery was formed by the right vertebral artery alone; at the upper border of the pons, the basilar artery curved to the right behind the right mam-

TABLE 1
SUMMARY OF 41 REPORTED CASES OF HEMIBALLISM

Author	Year	Age	Sex	Laterality		Destruction of Corpus Luysi	
				Right	Left	Complete	Partial
Greiff [22]	1883	78	F		+	+	
Canfield and Putnam [42]	1884	59	M	+		+	
Touche [55]	1901	?	F	+		+	
von Economo [45]	1910	71	M		+	+	
Fisher [20]	1911	72	F		+	+	
Bremme [40]	1919	40	F	+			+
Campora [41]	1922	78	F		+		+
Jakob, A.[45] (case 19)	1923	75	F		+	+	
Martin [1]	1927	62	M	+			+
Matzdorff [51]	1927	80	F		+		+
Jakob, C. [49]	1928	59	F		+	+	
von Santha [12]	1928	77	F	+			+
Wenderowic [24]	1928	81	F		+		+
Pelnar and Sikl [58]	1929	72	F		+	+	
Balthasar [2]	1930	65	F		+		+
Bonhoeffer [39]	1930	52	F	+		+	
Uiberall and Samet-Ambrus [56]	1931	56	M		+		+
von Santha [13]	1932	57	F	+			+
Wulff [57]	1932	51	F		+		+
Bertrand and Garcin [16]	1933	61	F		+	+	
Bodechtel and Hikl [26]	1934	50	M		+	+	
Martin and Alcock [11]	1934	56	M		+		+
Juba and Rakonitz [25]	1937	65	M		+		+
Drouet et al.[44]	1938	62	M		+	+	
Gregory [47]	1938	68	F	+		+	
Marcus and Sjögren [14] (case 1)	1938	71	M	+		+	
Kutsch [50]	1939	64	F	+			+
Moersch and Kernohan [52]	1939	65	M		+		+
Bertrand and Christophe [17]	1942	73	F	+		+	
Kelman [15]	1945	66	M		+	+	
Christensen and Krabbe [43]	1945	69	F		+	+	
Lea-Plaza and Uiberall [32]							
(case 2)	1945	65	F		+	+	
(case 3)		56	M		+	+	
Potts [54]	1946	60	M	+		+	
Thurel and Grenier [6]	1947	73	M		+	+	
Puharich and Friedman [7]	1948	79	M		+		+
Garcin et al.[8]	1949	73	F		+	+	
Rostowski and Robertson [9]							
(case 1)	1950	48	F	+		+	
(case 2)		75	F	+		+	
Pfeil [5]	1952	73	M		+	+	
Jech and Seitelberger [10]	1953	70	M	+			+

millary body prior to dividing into two posterior cerebral arteries. The left posterior cerebral artery was thus definitely longer than the right. Ballism occurred on the right side due to a lesion in the left subthalamic nucleus. Jech and Seitelberger[10] reported a vascular anomaly of the circle of Willis in which the right posterior cerebral artery was of very small caliber. However, since the subthalamic lesion was present on the left, the importance of this variation can be questioned. This same patient had previously sustained a thrombosis of the right posterior inferior cerebellar artery.

It would seem that a study of the vascular pattern in such cases might be worthwhile, since almost all of the lesions associated with ballism are of a vascular necrotizing nature. Ballistic activity[18] usually is reported to be most marked in the upper extremities (55 per cent of the cases), though it may be of equal severity in the upper and lower limbs. Abnormal involuntary activity in the facial musculature was reported in 64 per cent of the 31 cases studied. Evaluation of activity in the facial musculature is difficult in most cases, since grimacing and facial contortions may be of a voluntary nature associated with a conscious effort on the part of the patient to limit the violence and forcefulness of appendicular activity. Involvement of the axial muscula-

ture apparently is unusual, having been reported in only 13 per cent of these 31 cases.

There is some question concerning the particular blood vessels whose branches supply the subthalamic nucleus. This structure, like others in the brain and elsewhere, probably has a variable source of blood supply. The major vessels considered most likely to supply the subthalamic nucleus indirectly are the posterior communicating artery, the posterior cerebral artery, and branches from the interpeduncular plexus which receives communications from these two major vessels. Foix and Hillemand[28] stated that the corpus Luysi was irrigated by branches of the anterior chorioidal, the posterior communicating, and the posterior cerebral arteries. Moniz[29] felt that the major source of blood supply for this nucleus was derived from branches of the posterior cerebral artery, but that some branches of the anterior chorioidal artery also nourished the nucleus. Abbie[30] on the basis of vascular injection studies has stated that branches of the anterior chorioidal artery sometimes supply the subthalamic nucleus, the red nucleus, and the substantia nigra, but recent human studies and experiments with adult chimpanzees,[31] in which this vessel was ligated and divided by electrocoagulation, did not reveal significant changes in the subthalamic nucleus. These results do not preclude the possibility that branches of the anterior chorioidal artery may supply the subthalamic nucleus, but rather indicated that the significance of the blood supply from this source is minor in comparison to the contribution from other vessels. These authors have considered particularly patterns of vascular failure in the central nervous system and their studies have helped to explain the rather wide discrepancies in considered primary zones of supply for particular cerebral vessels obtained by 1) injections of individual blood vessels of fresh brains and 2) surgical ligation of selected arteries during life. They have suggested that the region in question (junction of the diencephalon and mesencephalon) may be especially vulnerable because it represents a junctional area supplied rostrally by the carotid artery and its branches and caudally by the vertebral-basilar system. The opinion of Moniz that the subthalamic nucleus is primarily supplied by branches of the posterior cerebral artery seems to be supported by available pathologic evidence. This vessel was said to have been the source of hemorrhage in a case (number 2) reported by Lea-Plaza and Uiberall[32] and was thrombosed in the case of Jech and Seitelberger.[10] Other cases[7,15,33,34] suggest that ballism may be associated with vascular pathology involving the posterior cerebral artery and its branches, since softenings were found in its field of distribution and homonymous field defects were present in at least two of these cases.

In regard to somatotopic localization within the human subthalamic nucleus, a recent study[18] disclosed no correlation between ballistic activity in the extremities and destruction of various portions of the subthalamic nucleus. In most instances (the case of Marcus and Sjögren[14] is an exception) if a sufficient portion of the nucleus is destroyed to produce ballism, both upper and lower extremities are involved but not always to an equal extent. It appears impossible therefore to distinguish clinically between complete and partial destruction of the corpus Luysi. Other data regarding possible somatotopic relationships within the subthalamic nucleus have been mentioned previously.

An interesting observation from experimental studies of the rhesus monkey was that abnormal involuntary activity involving the facial, glossal, cervical, and deglutitional musculature was never observed as a consequence of stereotaxic lesions in the subthalamic nucleus. These experiments were done on 175 rhesus monkeys, of which 142 have been reported in the literature.[21–24] Also with few exceptions the activity has usually been most severe in the lower extremities. An inquiry into this question revealed certain significant findings. Sub-

thalamic hyperkinesia involving the upper extremity was never seen in the absence of activity in the lower extremity and hyperkinesia of the axial musculature appeared to be correlated with bilateral destruction of the subthalamic nucleus. Data relating to intranuclear somatotopic localization in the rhesus monkey were taken from 17 selected animals of a series of 48 exhibiting unequivocal and persistent choreoid activity until death, sacrifice, or further (ameliorative) surgery; all had lesions involving the subthalamic nucleus contralateral to the activity. In spite of relatively restricted localization, these stereotaxic lesions were not, except in a few instances, confined within the capsule of the subthalamic nucleus and no lesion completely destroyed the nucleus. Quantitative estimates of the total volume of the nucleus, the total volume of the lesion, and the percentile volumes of the lesion in the anterior, middle, and caudal thirds of the nucleus and in the medial and lateral halves of the nucleus were made according to the method of Dornfeld, Slater, and Scheffé[26] by projecting, drawing, and measuring serial sections with a planimeter. From these data planimetric profiles were constructed from which volumetric data were obtained by further measurements and calculations. Resulting data seemed to indicate that dyskinesia in the lower extremity was related to destruction of the rostral part of the subthalamic nucleus, while destruction of the caudal portion of the nucleus was related to activity in the upper extremities. With the stereotaxic method it was impossible to produce a lesion in the caudal portion of the nucleus without producing some damage in the rostral part of the nucleus; but a lesion of the rostral part of the nucleus could be made without damage to the caudal part. This theory was thought to explain the particularly common occurrence of subthalamic hyperkinesia in the lower extremities in these monkeys. Further stereotaxic studies using other approaches to this structure might confirm this theory.

In the currently reported case planimetric profiles and volumetric data were obtained for the subthalamic nucleus according to the methods described above. The lesion of the subthalamic nucleus occupied the lateral half of the nucleus rostrally and the dorsal half of the nucleus in more caudal sections. It is perhaps possible that some relationship might exist between destruction of the rostral portion of the nucleus and activity in the cervical musculature, but such a conclusion based on this case seems unwarranted. Estimated volumes of the subthalamic nuclei (right, 101 cu. mm.; left, 118 cu. mm.) were significantly smaller than determinations obtained from other brains. Von Bonin and Shariff's[35] estimation of the volume of the subthalamic nucleus of the human of 157.7 cu. mm. was very close to our own determination of 159.7 cu. mm. obtained from brain T-9 (photographs of which were published by Riley[36]). Volumetric determinations indicated that approximately 31 per cent of the right subthalamic nucleus was destroyed in this case. This would seem to indicate that the limit of physiologic safety[37] for the human subthalamic nucleus (that is, the maximal pro-

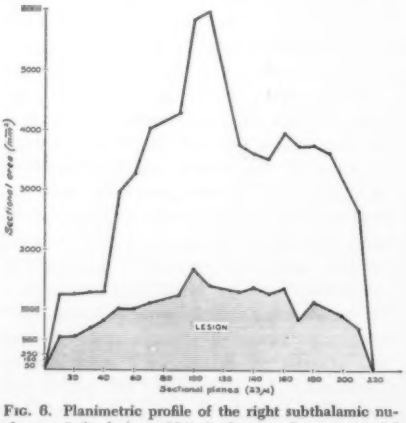


FIG. 6. Planimetric profile of the right subthalamic nucleus and the lesion within it showing the rostrocaudal disposition. No attempt was made to smooth the resulting curve. Approximately 31 per cent of the total volume of the nucleus was destroyed.

portion of nuclear destruction which would not provoke detectable neurologic deficit) is of the same order as that found in the rhesus monkey. The limit of physiologic safety for the subthalamic nucleus of the rhesus monkey has been estimated to be about 20 per cent, though it may be somewhat less.

One of the most interesting features of the case reported here is that the ballism disappeared after ventrolateral cordotomy at the level of the third cervical segment. Because of inadequacies in the material available for study, it cannot be stated that the activity vanished as a result of surgical treatment, nor can it be stated which structures were interrupted. If disappearance of the dyskinesia was related to surgery, it would seem of particular importance that this be confirmed, not only because the prognosis for patients with ballism is notoriously poor, survival being about six weeks after onset, but because it would increase our general knowledge of the neuroanatomic and neurophysiologic mechanism of these dyskinesias.

The possibility that disappearance of the dyskinesia may have been due to a second vascular lesion should not be overlooked. Indeed, it is possible that the lesion in the region of the globus pallidus may have occurred after the initial lesion. Experimental studies have indicated that lesions of the dorsal division of the ansa lenticularis and/or of the globus pallidus can ameliorate or abolish subthalamic hyperkinesia in the monkey.[23]

SUMMARY AND CONCLUSIONS

A case of ballism occurring in a 72 year old hypertensive male controlled after ventrolateral cordotomy was reported clinically and pathologically. Death resulted from bronchopneumonia 23 days after onset of the dyskinesia. Sections of the brain were studied by the Marchi method. The lesion, destroying approximately 31 per cent of the right subthalamic nucleus, was located in the lateral half of the nucleus rostrally and in the dorsal half of the nucleus caudally. No definite conclusion regarding somatotopical localization within the subthalamic nucleus could be drawn from this case.

The following conclusions were drawn:

1. The limit of physiologic safety for the human subthalamic nucleus is of the same order as in the rhesus monkey despite its absolute size, being approximately 15 times as large (relative size is about the same).

2. Preexisting striatal deficit contralateral to a lesion of the subthalamic nucleus apparently does not prevent the appearance of ballism in man.

3. The primary blood supply of the subthalamic nucleus is probably derived from branches of the posterior cerebral artery.

4. The possibility that localized lesions of the spinal cord may abolish ballistic activity without producing signs or symptoms of pyramidal deficit is suggested by the case reported here. An attempt to confirm this result would seem worthwhile.

HISTORICAL NOTE

The term hemiballism is said to have been coined by Kussmaul (Greidenberg, von Monakow, H. Oppenheim, Jakob, (A), and Herz; see Whittier[8]) but Moersch and Kernohan, Whittier, and subsequent authors have been unable to find the term in any of Kussmaul's published works. The term hemiballism first appears in the Index Catalogue of the Library of the Surgeon General's Office in the Fourth Series, volume 7, page 492. Under this heading, it reads: see chorea, unilateral. Prior to the use of the term here, neither ballism nor hemiballism is listed as a title or subtitle. In earlier references to chorea the term appears in the title of inaugural dissertations from the University of Vienna by Joann. Udalricus Pfefferkorn[58] (1833) and Henricus Hermannus Langer[59] (1838) as, "De Ballismo." Pfefferkorn states that ballismi (' . . . . . ,' saltare, to jump, to dance) is also referred to as Choreae Sancti Viti, which he understands to be a convulsive disease manifest by bodily movement and involuntary gesticulations which cease during sleep. He mentions that, "One does not come across traces of this disease in the writings of Hippocrates or in the early doctorate theses, unless one is willing to consider the condition, scelotyrben, as ballism." The thesis traces the historical background of the origin of the term Saint Vitus' dance forward from the year (1374) in which the plague

of the black death ended. Descriptions of the condition do not conform with present medical concepts. Finally Pfefferkorn wrote, "We are making use of the word ballism, which is the established custom in our clinic, after the example of Plouequet (rendered in Latin as "Plouquettum"). Professor Dr. Hans Hoff of the Neurologische Institut Wien graciously investigated Wilhelm Gottfried Plouequet (1744 to 1814) and found that he received his doctorate in medicine at the University of Tübingen and later became a professor there.

Langer uses the term ballismus (according to Swediaur) to mean: to jump, to dance and above all to throw, particularly to throw back and forth, especially of the legs. His long list of synonyms includes Morbus Sti. Viti, Morbus Sti. Modesti, Chorea lasciva (Paracelsum), and Choreomania (Plouequet) among others. The next reference to the term is that of Roberto Massalongo[60] (Docente Universita di Padova) in 1895, who used it as "Ballismo chronico." For this author ballismo cronico was synonymous with chronic progressive chorea, but his description of the dyskinesia bore certain resemblances to the type of activity which is now known to be associated with lesions of the corpus Luysi. The course of the disease was, however, very different. The author is indebted to Dr. John R. Whittier for making available certain material used in preparing this historical note.

The author is indebted to Dr. M. Hunter Brown (Westwood Village, Los Angeles, California) who provided the material for study and prepared the clinical summary. Unfortunately, cinematographic records were not made of the dyskinesia exhibited by this patient.

REFERENCES

1. Martin, J. P.: Hemichorea resulting from a local lesion of the brain (syndrome of the body of Luys), Brain 50:637, 1927.
2. Balthasar, K.: Ueber das Syndrom des Corpus Luys an Hand eines anatomisch untersuchten Falles von Hemiballismus, Ztschr. Neurol. u. Psychiat. 128:702, 1930.
3. Whittier, J. R.: Ballism and the subthalamic nucleus (nucleus hypothalamicus; corpus Luysi), Arch. Neurol. & Psychiat. 58:672, 1947.
4. Meyers, R., Sweeney, D. B., and Schwidde, J. T.: Hemiballismus: Aetiology and surgical treatment, J. Neurol., Neurosurg., & Psychiat. 13:115, 1950.
5. Pfeil, E. T.: Hemiballismus hemichorea following a lesion of the corpus Luysi, J. Nerv. & Ment. Dis. 116:36, 1952.
6. Thurel, R., and Grenier, J.: Hemichorée avec hémiballisme: Hémorragie limitée an corps de Luys du côte opposé, Rev. neurol. 79:502, 1947.
7. Puharich, H. K., and Friedman, M.: A clinical complex exhibiting left homonymous hemianopsia, the neocerebellar syndrome, hemiballismus and the anterior inferior cerebellar artery syndrome, Permanente Found. M. Bull. 4:208, 1948.
8. Garcin, R., Bertrand, I., Kipfer, M., Gruner, J., and Pestel, M.: Hemiballismus. Etude anatomo-clinique, Rev. neurol. 81:964, 1949.
9. Rostowski, J., and Robertson, R. F.: Hemihyperkinesia (Hemiballismus, hemichorea, hemipseudo-purposive movements), Edinburgh M. J. 62:478, 1950.
10. Jech, R. K., and Seitelberger, F.: Hemiballismus (Syndrome des Corpus Luysii); eine klinisch-anatomische Studie, Wien Ztschr. Nervenh. 6:169, 1953.
11. Martin, J. P., and Alcock, N. S.: Hemichorea associated with a lesion of the corpus Luysi, Brain 57:504, 1934.
12. Von Santha, K.: Zur Klinik und Anatomie des Hemiballismus, Arch. Psychiat. 84:664, 1928.
13. Von Santha, K.: Hemiballismus und Corpus Luysi (Anatomische und pathophysiologische Beiträge zur Frage des Hemiballismus nebst Versuch einer somatotopischen Lokalisation im Corpus Luysi), Ztschr. Neurol. u. Psychiat. 141:321, 1932.
14. Marcus, H., and Sjögren, H.: L'hemiballisine et le corpo de Luys, Rev. neurol. 70:1, 1938.
15. Kelman, H.: Hemiballismus: Clinicopathologic study of two cases, J. Nerv. & Ment. Dis. 101:363, 1945.
16. Bertrand, I., and Garcin, R.: Etude anatomo-clinique d'un cas d'hemiballismus: Lésion dégénérative du corps de Luys et de la zona incerta, Rev. neurol. 2:820, 1933.
17. Bertrand, I., and Christophe, J.: Etude anatomo-clinique d'un cas d'hemiballisme. Hémorragie lineaire du corps de Luys avec extension au locus niger, Rev. neurol. 74:140, 1944.
18. Carpenter, M. B., and Carpenter, C. S.: Analysis of somatotopic relations of the corpus Luysi in man and monkey. Relation between the site of dyskinesia and distribution of lesions within the subthalamic nucleus, J. Comp. Neurol. 95: 349, 1951.
19. Morgan, L. O.: Symptoms and fiber degeneration following experimental lesions in the subthalamic nucleus of Luys in the dog, J. Comp. Neurol. 44: 379, 1927.
20. Glees, P., and Wall, P. D.: Fiber connections of the subthalamic region and the centromedian nucleus of the thalamus, Brain 69:195, 1946.
21. Whittier, J. R., and Mettler, F. A.: Studies on the subthalamus of the rhesus monkey. I. Anatomy and fiber connections of the subthalamic nucleus of Luys, J. Comp. Neurol. 90:281, 1949a.
22. Whittier, J. R., and Mettler, F. A.: Studies on the subthalamus of the rhesus monkey. II. Hyperkinesia and other physiologic effects of subthalamic lesions, with special reference to the subthalamic nucleus of Luys, J. Comp. Neurol. 90:319, 1949b.
23. Carpenter, M. B., Whittier, J. R., and Mettler, F. A.: Analysis of choreoid hyperkinesia in the rhesus monkey. Surgical and pharmacological

analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of Luys, J. Comp. Neurol. 92:293, 1950.
24. Carpenter, M. B., and Mettler, F. A.: Analysis of subthalamic hyperkinesia in the monkey with special reference to ablations of agranular cortex, J. Comp. Neurol. 95:125, 1951.
25. Juba, A., and Rakonitz, E.: Ueber einen Fall von Hemiballismus (Beitrag zur Somatotopie des Corpus Luysi), Arch. Psychiat. 106:629, 1937.
26. Dornfeld, E. J., Slater, D. W., and Scheffe, H.: A method for accurate determination of volume and cell numbers in small organs, Anat. Rec. 82:255, 1942.
27. Mettler, F. A.: Neuroanatomy, St. Louis, C. V. Mosby Co., 1948.
28. Foix, C. H., and Hillemand, P.: Notes sur la désposition générales des artèrés de l'axe encephalique, Compt. rend. Soc. biol. 92:31, 1925.
29. Moniz, E.: Hemiballismo: A proposito de tres casos, Lisboa méd. 8:481, 1931.
30. Abbie, A. A.: The clinical significance of the anterior chorioidal artery, Brain 56:233, 1933.
31. Mettler, F. A., Cooper, I. S., Liss, H., Carpenter, M. B., and Noback, C. R.: Patterns of vascular failure in the central nervous system, J. Neuropath. & Exper. Neurol. 13:528, 1954.
32. Lea-Plaza, H., and Uiberall, E.: Hemiballismo, Rev. med. Chile 73:938, 1945.
33. Greiff, F.: Zur Localisation der Hemichorea, Arch. Psychiat. 14:598, 1883.
34. Wenderowic, E.: Ueber das anatomische Substrat des Hemiballismus bzw. der Hemichorea, Ztschr. Neurol. u. Psychiat. 114:78, 1928.
35. von Bonin, G., and Schariff, G. A.: Extrapyramidal nuclei among mammals: A quantitative study, J. Comp. Neurol. 94:427, 1951.
36. Riley, H. A.: An Atlas of the Basal Ganglia, Brain Stem and Spinal Cord, Baltimore, Williams & Wilkins Co., 1943, pp. 243-317.
37. Meltzer, S. J.: The factors of safety in animal structures and animal economy, Harvey Lectures, 139-169, 1906-07.
38. Bodechtel, G., and Hikl, W.: Hemiballismus bei doppelseitiger Schädigung des Corpus Luysii, Arch. Psychiat. 102:654, 1934.
39. Bonhoeffer, K.: Klinische und anatomische Beiträge zur Pathologie des Sehhügels und der Regio subthalamica, Monatsschr. Psychiat. u. Neurol. 77: 127, 1930.
40. Bremme, H.: Ein Beitrag zur Bindarmchorea, Monatsschr. Psychiat. u. Neurol. 45:107, 1919.
41. Campora, G.: Sopra un caso di emicorea con reperto necroscopico, Pathologica 14:41, 1922.
42. Canfield, R. M., and Putnam, J. J.: A case of acute hemiplegic chorea with autopsy remarks, Boston M. and Surg. J. 111:220, 1884.
43. Christensen, E., and Krabbe, K. H.: Case of hemiballism with autopsy, Acta psychiat. et neurol. 20:147, 1945.
44. Drouet, P. L., Michon, P., Lepoire, F., and Beau: Syndrome d'hémiballisme. Bull. et mém. Soc. méd. hôp. Paris 54:1085, 1938.
45. von Economo, C. J.: Beitrag zur Kasuistik und zur Erklärung der posthemiplegischen Chorea, Wien klin. Wchnschr. 23:429, 1910.
46. Fischer, O.: Zur Frage der anatomischen Grundlage der Athétose double und der posthemiplegischen Bewegungsstörung überhaupt, Ztschr. Neurol. u. Psychiat. 7:463, 1911.
47. Gregory, H. S.: A case of hemiballismus, New York State J. Med. 38:635, 1938.
48. Jakob, A.: Die Extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, p. 174-183.
49. Jakob, C.: Sindrome de hemibalismo coreiforme cruzado por hemorragia en al nucleo hipothalamico, Arch. argent. neurol. 2:1, 1928.
50. Kutsch, T.: Ein Beitrag zur Lokalisation des Hemiballismus, Ztschr. Neurol. u. Psychiat. 164: 404, 1939.
51. Matzdorff, P.: Beiträge zur Pathologie des extrapyramidal motorischen Systems; Das Syndrom des Corpus Luysi, Ztschr. Neurol. u. Psychiat. 109:538, 1927.
52. Moersch, F. P., and Kernohan, J. W.: Hemiballismus: A clinicopathological study, Arch. Neurol. & Psychiat. 41:365, 1939.
53. Pelnar, J., and Sikl, H.: L'hémiballisme, le ballisme aigu et le corps de Luys, Rev. neurol. 2: 328, 1929.
54. Potts, F.: Syndrome of hemiballism: Anatomicoclinical study of case, Rev. cubana neurol. g. psiquiat. 1:28, 1946.
55. Touche: Deux cas d'hémichorée organique avec autopsie, Rev. neurol. 9:1080, 1901.
56. Uiberall, H., and Samet-Ambrus, V.: Ein Beitrag zur Kenntnis des Hemiballismus, Ztschr. Neurol. u. Psychiat. 131:502, 1931.
57. Wulff, H.: Corpus Luysi und das hemiballistische Syndrom, Acta psychiat. et neurol. 7:999, 1932.
58. Pfefferkorn, J. W.: De Ballismo, Inaug. Dissert. Vindobonae, Antonii Strauss, 1833, 34 pp.
59. Langer, H. H.: De Ballismo, Inaug. Dissert. Viennae, Antonii Pichler, 1838, 22 pp.
60. Massalongo, R.: Ballismo cronico; contributo alla patologia delle coree, Policlinico 2:481, 1895.

Swelling of Damaged Brain Tissue

Ricardo F. S. Edstrom, M.D. and Hiram E. Essex, Ph.D.

THE BRAIN is known to swell after death through absorption of fluid, both in the skull[1–3] and in vitro.[1,2,4–6] This capacity to absorb fluid is of practical importance in the study of cerebral edema, in which most measurements are made on material obtained at necropsy. Among accepted methods[7] in this field of research are determinations of brain weight or volume in relation to skull capacity, measurements of water content of cerebral tissue, and evaluations of the histologic appearance of sections of the brain. These methods are all affected by agonal and postmortem changes, but to what extent little is known. The present study is concerned with the rapidity and extent of this change, as it can be measured by weighing brains removed quickly or after some delay following decapitation.

MATERIAL AND METHODS

A total of 355 apparently healthy guinea pigs were used. For reasons discussed later, all were males of 800 to 1,000 gm. body weight. They were obtained from the same colony which had been inbred for many years. Their routine care was unchanged during the study. All brains were removed by the same observer using a uniform technic, and care was taken to include identical anatomic structures in all cases. The animals were killed by decapitation; the medulla was then cut through the atlanto-occipital interspace; the optic nerves were cut close to the chiasm, and the olfactory bulbs and the largest vessels on the base of the brain were removed before the specimen was weighed. In the animals of the control groups, that is, the groups in which the brains were weighed as soon as possible after death, the time from decapitation until the brain was on the scales usually ranged from three to five minutes. In the experimental groups, the animals' heads were left at room temperature with the brain in situ for varying lengths of time, as shown in table 1, and then the brains were removed and weighed with the same rapid technic as used with the controls.

A preliminary study has shown that male guinea pigs have significantly heavier brains than females, and that heavier animals have heavier brains than lighter animals. For these reasons, in order to insure greater uniformity of the brain weights, male guinea pigs weighing 800 to 1,000 gm. were used exclu-

From the sections of neurology and physiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

TABLE 1

MEAN BRAIN WEIGHT OF MALE GUINEA PIGS IN RELATION TO TIME OF REMOVAL FROM SKULL

	Body weight, gm.									
	800–849		850–899		900–949		950–999		*Total*	
	Number	*Brain weight*	*Number*	*Brain weight*	*Number*	*Brain weight*	*Number*	*Brain weight*	*Number*	*Brain weight*
Immediately removed brains										
Control 1	42	3.98	39	3.99	33	4.02	34	4.03	148	4.00 ± 0.017*
Control 2	11	3.89	8	3.97	1	4.19	—	—	20	3.94 ± 0.037
Control 3	9	3.91	12	3.96	10	4.08	10	4.14	41	4.02 ± 0.037
All controls	62	3.95	59	3.98	44	4.04	44	4.05	209	4.00 ± 0.014
Removal of brain delayed										
5 to 30 minutes	15	4.17	12	4.19	11	4.07	7	4.16	45	4.15 ± 0.034
30 to 60 minutes	12	4.10	13	4.28	9	4.18	9	4.09	43	4.17 ± 0.032
1 to 2 hours	11	4.11	9	4.21	6	4.16	5	4.28	31	4.18 ± 0.028
2 to 3 hours	8	4.22	9	4.11	7	4.28	3	4.28	27	4.21 ± 0.038

*The figure after the ± is the standard error of the mean.

sively. Even within this range of weight the study showed a small influence of body weight on brain weight (table 1). The animals were therefore stratified with respect to body weight of animal, so that the distribution of and average body weight for the different time groups should be approximately the same. After this precaution was taken, the possible influence of body weight was disregarded.

It is conceivable that changes in the guinea pig population or in the observer's technic might occur with time. Therefore, during the six months this study was in progress, control groups were studied repeatedly. "Control 1" refers to a group measured at the beginning of the study (February-March), "control 2" was done in May, and "control 3" was taken at the end of the study (July-August). As can be seen in the table, the passage of time did not greatly influence the results obtained.

RESULTS

When the brains were grouped according to the time they had remained in the separated head, as shown in table 1, and the mean weights of the brains were plotted against time, the curve shown in figure 1 resulted. From these data it is evident that after decapitation a very rapid gain in the weight of the guinea pig's brain occurs which amounts to about 4 per cent of the initial brain weight within 30 minutes.

The difference in weight between the brains removed immediately (controls) and those excised after five to 30 minutes' delay was 0.15 ± 0.035 gm., which is obviously statistically significant. After half an hour following death, the brain weight continues to increase during the postmortem period studied (two to three hours). This increase, though at a much slower rate than in the period immediately following decapitation, is also statistically significant.*

COMMENT

It has been shown previously that the brain swells after death, probably through absorption of cerebrospinal fluid.[1–3] It is assumed that the gain in weight demonstrated in this paper is

*On the basis of a test of the regression coefficient referring to change of brain weight with time.

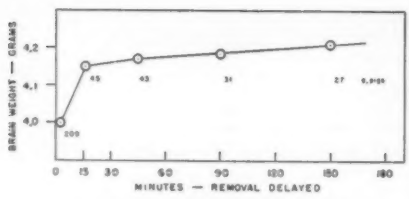


FIG. 1. Effect of delayed removal on weight of brains of male guinea pigs weighing 800 to 1,000 gm.

due to the same mechanism. The rapidity of this change in weight, as far as we know, has not been previously recognized. There is reason to believe that part of the initial swelling occurs at the time of, or even preceding, the death of the brain cells. It is a well-known fact that arrest of the blood supply of the brain does not lead to irreversible nerve cell damage until after several minutes. Thus complete tissue death cannot have occurred at the time the brains of the control groups were removed from the skull. This conclusion was supported by the observation that, as a rule, when the trigeminal nerves were cut in the course of lifting the brain out of the skull, the guinea pig's jaw could be seen to move. It is therefore evident that an immediate effect of injury to brain tissue is absorption of fluid and consequent swelling. It is not proved that the damage has to be irreversible for swelling to take place.

It has previously been held[1–3] that hours or days had to pass after death before the brain could expand to any significant extent, and the brains of larger species are known to swell more slowly than those of small animals.[1] These observations seem to characterize the swelling which occurs after complete tissue death, and probably correspond to the part of the curve in figure 1 representing the later slow changes of the brain weight. The evidence obtained in this study indicates that the time of most rapid absorption of fluid is immediately after injury to brain tissue. Thus no conclusions about increased water content or brain volume in the living state should be drawn from postmortem findings, unless agonal and postmortem fluid absorption is taken into account.

The histologic appearance of the brain changes rapidly after death in the direction of cell expansion, as has been shown for glia,[8] as well as nerve cells.[9,10] Using a nondehydrating technic, Zülch reported that the interstitial fluid was rapidly absorbed by the nerve cells after removal of brain tissue. This seems to explain the finer mechanism of the rapid gain in weight of the brain found in the present study: the damaged cells absorb the tissue fluid and later probably the cerebrospinal fluid, a process which results in a gain in weight of the brain.

It is conceivable that when brain tissue is damaged locally in the living individual, a swelling of the brain might be caused through the same mechanism: the injured cells absorb the interstitial fluid, which will be continuously replaced from the circulating blood, as long as the pressure relations are such as to permit further expansion. Thus a form of intracellular cerebral edema might be produced.

SUMMARY AND CONCLUSIONS

The brain of the guinea pig has been shown to increase about 4 per cent in weight within 30 minutes after decapitation. Later the gain in weight continues at a very much slower rate for several hours. This increase in weight of the brain is presumably an effect of fluid absorption. The initial rapidity of

this phenomenon appears not to have been fully appreciated previously.

Implications of these findings in studies of volume and water content of brains removed at necropsy are discussed.

Local injury to cerebral tissue is mentioned as a possible factor in the formation of cerebral edema in vivo.

The authors wish to express their gratitude to Dr. Joseph Berkson for valuable help with the statistical problems involved in this study.

REFERENCES

1. Haussler, Georg: Hirndruck: Hirnödem—Hirnschwellung, Zentralbl. Neurochir. 2:247; 328, 1937.
2. White, J. C., Verlot, M., Selverstone, B., and Beecher, H. K.: Changes in brain volume during anesthesia: The effects of anoxia and hypercapnia, Arch. Surg. 44:1, 1942.
3. Zulch, K. J.: Hirnödem, Hirnschwellung, Hirndruck, Zentralbl. Neurochir. 11:350; 12:174; 365, 1952.
4. Alexander, Leo, and Looney, J. M.: Physicochemical properties of brain, especially in senile dementia and cerebral edema: Differential ratio of skull capacity to volume, specific weight, water content, water-binding capacity and pH of the brain, Arch. Neurol. & Psychiat. 40:877, 1938.
5. Jorns, G.: Ueber das Hirnödem, Zentralbl. Neurochir. 2:58, 1936.
6. Selbach, Ottilie C., and Selbach, Helmut: Die Hirnvolumen-Vermehrung als Problem der physikalischen Chemie des Hirngewebes, Allg. Ztschr. Psychiat. 125:137, 1949.
7. Greenfield, J. G.: Discussion on cerebral oedema, Proc. Roy. Soc. Med. 40:695, 1947.
8. Penfield, Wilder: Neuroglia: Normal and pathological. In: Cytology & Cellular Pathology of the Nervous System. New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 423-479.
9. Ferrero, C.: Altérations du système nerveux central après la mort: Remarques sur les conclusions d'un travail de *Camerer*, Monatsschr. Psychiat. u. Neurol. 113:118, 1947.
10. Koenig, Ruth S., and Koenig, Harold: An experimental study of post mortem alterations in neurons of the central nervous system, J. Neuropath. & Exper. Neurol. 11:69, 1952.

■ I have ascertained that after almost a complete transverse section of the spinal cord, leaving undivided only the posterior columns, the transmission of sensitive impressions from almost all the parts of the body behind the section does not take place. This experiment, performed by Stilling almost exclusively upon frogs, led him to affirm that sensibility is then entirely lost in all the parts behind the section. Messrs. Vulpian and Philipeaux, who made this experiment some time after Schiff, positively declare that sensibility is completely and definitely lost. I have ascertained that the differences in the results of this experiment depend upon various circumstances. At first, if the least quantity of the central gray matter of the spinal cord is left undivided, sensibility persists (although much diminished) almost everywhere behind the section. Besides, there are parts in the neighborhood of the section, and behind it, which always remain sensitive.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Diagnosis and Surgical Therapy of Chronic Midline Cervical Disk Protrusions

Eric T. Yuhl, M.D., Duke Hanna, M.D., Theodore Rasmussen, M.D. and Richard B. Richter, M.D.

CHRONIC LOW GRADE COMPRESSION of the spinal cord due to midline protrusion or bulging of one or more cervical intervertebral disks often presents a serious problem in diagnosis and treatment. It is the purpose of this report to describe our clinical experiences in a series of 32 consecutive patients operated on for the syndrome of chronic compression of the cervical spinal cord due to longstanding intervertebral disk protrusion or bony ridges secondary to such protrusions, so-called "hypertrophic osteoarthritis of the spine."

Cervical disk herniations may be divided into three types: 1) lateral protrusion, 2) acute midline protrusion, and 3) chronic midline protrusion. Lateral protrusions, which comprise the largest group of the three,[36] produce the signs and symptoms of compression of one or more cervical nerve roots. This syndrome has been well documented in the literature.[12,25,28,33,37,40,46,47] Acute midline protrusions, the rarest of the three types,[15] produce signs and symptoms similar to the symptoms of intraspinal neoplasm and do not present a difficult diagnostic problem.[5,13] This report will deal solely with the third group, chronic midline protrusions. An excellent historic review is given by Brain and co-workers[10] in their report of a series of 45 cases.

The fact that mechanical protrusion of intervertebral disk substance could produce spinal cord damage was well described in the veterinary medical literature by Dexler[17] in 1896, long before it was recognized as a clinical entity in man. Olson and Hansen[31] in 1952 presented an excellent review of the signs, symptoms, and morbid anatomy of this lesion in the dog, with a review of the veterinary literature and a description of a surgical treatment.

In man these extradural masses were described as neoplasms in early reports,[2, 18,19,41] although Adson[3] in 1925 speculated on the role of trauma in producing these lesions (" . . . . in two specific instances of this series trauma was in-

From the divisions of neurological surgery and neurology, University of Chicago Clinics, Chicago.

strumental in the development of a fibrochondroma; it is likely, also, to have been the cause of the hypertrophic osteitis reported in seven of the cases which produced a narrowing of the spinal canal and consequent pressure on the cord and paralysis."). It is of interest that the role of trauma in precipitating symptoms in a patient with such a spinal lesion as well as its successful surgical treatment was described in 1901.[44] The laminectomy had been carried out by Horsley in 1892.

Peet and Echols[32] in 1934 were the first to point out that herniation of the intervertebral disk may cause compression of the spinal cord, although Dandy[14] in 1929 reported two cases of intraspinal protrusion of disk material with compression of the cauda equina. A subsequent report by Mixter and Ayer[29] described eight cases of midline hernias of cervical disk producing the signs and symptoms of spinal cord compression. Since then, the reports of Hawk,[23] Epstein and Davidoff,[20] and others[4,7,16,21,22,27,30,35,38,39,42,43] have materially added to the description of this syndrome.

The clinical material in this series consists of 32 patients with signs and symptoms of chronic spinal cord disease associated with ridges or humps across the ventral aspect of the cervical spinal canal at one or more disk levels who were operated upon at the University of Chicago Clinics between July 1948 and February 1954.

The youngest patient in this group was 43 years of age and the oldest was 69. There were ten females and 22 males. The majority of the females were housewives. The occupations of the male patients ranged from sedentary clerical work to active heavy labor.

The cases were reviewed in regard to 1) symptoms, 2) neurologic findings, 3) examinations of the cerebrospinal fluid, 4) plain radiographic examinations of the cervical spine, 5) myelographic examinations, 6) findings at operations, and 7) follow-up results.

SYMPTOMS

The prominent symptoms presented by these patients were weakness of one or more extremities, pain either localized to the neck or of a radicular nature, paresthesias of varying distribution, and ataxia.

Weakness: Each of the 32 patients complained of motor weakness. In five patients the weakness was restricted to one upper extremity; in two patients the weakness was noticed in both upper extremities; in three patients the weakness involved both legs; and 13 of the patients complained of weakness in all four extremities. The remaining nine patients had various other combinations of weakness. In all instances the patient stated that the weakness had become progressively worse since the onset of the illness. In eight of the 32 patients the symptom of motor weakness had been present for less than six months, and in each of these instances the weakness had become precipitously more severe. In the remaining patients weakness had been present for an average of one year except for one patient who had noted slowly increasing weakness for over a period of 12 years.

Paresthesia: Twenty-one of the 32 patients (69 per cent) complained of sensory disturbances varying from intermittent sensations of numbness or tingling localized to one or several digits, to complete and profound generalized anesthesia of the trunk and lower extremities. Five of the 21 patients had numb-

ness or tingling sensations localized to one or two dermatome segments of one upper extremity. In three patients both upper extremities were involved. Two patients complained of numbness of one entire half of the trunk and corresponding extremities, and three had paresthesias involving all four extremities as well as the entire trunk. The remaining eight patients had various combinations of involvement.

Ataxia and incoordination: Eighteen (56 per cent) patients complained of clumsiness, incoordination, or disturbances of gait. Ataxia of gait was noticed by 16 patients and in most instances was severe. Clumsiness limited to one upper extremity was noted by one patient. The remaining patient complained of awkwardness and incoordination of both upper extremities.

Pain: Seventeen (53 per cent) of the 32 patients had no pain at any time. Seven of the 15 patients who did complain of pain at some stage of their illness had pain localized to the neck or associated with suboccipital and/or shoulder pain. One patient complained of unilateral radicular pain in the arm and one patient had bilateral radicular pain. The remaining six patients complained of vague and nonspecific pain involving the low back and either or both lower extremities, as well as vague pain in the upper extremities. In no instance, however, was the pain severe, nor was it the predominant complaint.

Miscellaneous: Two patients had considerable difficulty with constipation and one patient associated urgency with the onset of the illness. Incontinence was present in but one instance, and that patient was incontinent of both stool and urine.

Involuntary spasms or cramping of the musculature of the extremities was relatively infrequent. Three patients had involuntary spasms involving both legs. In one patient, spasms were present in one arm and one leg. Three patients complained of nonspecific cramping sensations in one or more extremities.

NEUROLOGIC FINDINGS

Disturbances of neurologic function have been divided into two groups: 1) those due to local involvement of one or more cervical nerve roots, and 2) those due to compression of the cervical spinal cord.

Involvement of the cervical nerve roots was manifested by depression or loss of deep tendon reflexes, sensory disturbances localized to one or more dermatome distributions, and atrophy of specific muscle groups in the upper extremities. Twelve of the 32 patients (37 per cent) exhibited atrophy of the musculature of one or both upper extremities. In six patients hypesthesia and hypalgesia were present in one or both upper extremities. In most instances the sensory loss was limited to a single dermatome. Depression or absence of a deep tendon reflex was noted in only three of the 32 patients.

Signs referable to the spinal cord were predominantly related to disturbances in the function of the corticospinal tracts and posterior columns. Twenty-three patients (72 per cent) exhibited spasticity and weakness of both lower extremities. Hyperactivity of the deep tendon reflexes was present in 28 patients (88 per cent). Extensor plantar responses were elicited bilaterally in 14 patients and unilaterally in six patients. Unilateral or bilateral ankle clonus was present in ten patients.

Disturbances in the function of the

posterior columns were present in 18 patients (56 per cent). Each of these patients had ataxia. Twelve patients had loss of vibratory sensation and eight had disturbances in position sense. The Romberg sign was positive in four patients.

Only seven patients had relative sensory levels elicited by pinprick. These levels were usually localized to a level between the second and sixth thoracic dermatome. Alterations in temperature sensation were demonstrated in two patients.

CEREBROSPINAL FLUID FINDINGS

Myelography was carried out in each of the 32 patients prior to operation, and the spinal fluid obtained at this time was examined with respect to the presence of cells, chemical constituents, and serologic tests for syphilis.

In this clinic 50 mg. per cent of total cerebrospinal fluid protein is considered the upper limit of normal. The protein was below 50 mg. per cent in 15 patients, and varied from 50 to 89 mg. per cent in 12 patients and from 90 to 134 mg. per cent in three. In the remaining two patients the protein was not recorded.

The other cerebrospinal fluid findings, cell counts, serologic tests for syphilis, and determinations of sugar and chloride were within normal limits in each patient.

RADIOGRAPHIC FINDINGS

The radiographic studies of the cervical spine included stereoscopic films in the anteroposterior, lateral, and right and left oblique projections. These radiographs were reviewed as to alterations in the curvature of the spine, narrowing of the intervertebral interspaces, and presence of osteophytic spur formation either anteriorly, posteriorly, or encroaching upon the intervertebral foramina.

In 20 (63 per cent) of the 32 patients the curvature of the cervical spine was altered. In 15 patients the alteration consisted of straightening of the normal cervical curve, and in five patients varying degrees of reversal of the normal curvature were observed.

In 20 patients narrowing of several intervertebral spaces was present. In seven of the remaining patients the narrowing was limited to a single interspace, and in five patients there was no narrowing of the intervertebral spaces. Six patients had nearly complete loss of interspace at one level.

The presence of posterior or posterolateral osteophytes on the vertebrae was the most constant finding and was present in all but one of the 32 patients. In the majority of instances these osteophytes were present at more than one level. The presence and size of anterior osteophytes varied considerably and did not correlate closely with the size and distribution of posterior osteophytes. Some degree of encroachment upon the intervertebral foramina was observed in all but one patient.

MYELOGRAPHIC FINDINGS

After injection of 12 to 15 cc. of Pantopaque for myelography, radiographs were made of the entire spinal canal. A sufficient number of films of the cervical region were made in the anteroposterior, lateral, and right and left oblique projections to visualize this region in all four projections.

In 30 patients myelography revealed central filling defects opposite the cervical intervertebral disks at more than

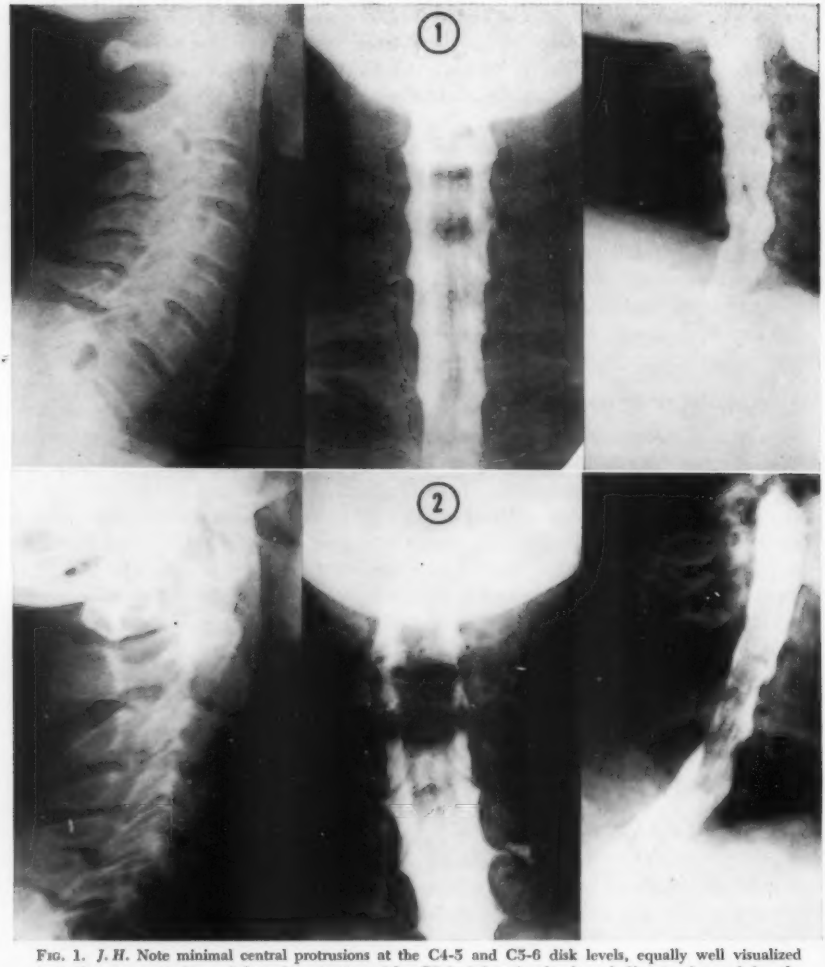


FIG. 1. *J. H.* Note minimal central protrusions at the C4-5 and C5-6 disk levels, equally well visualized in both anteroposterior and lateral projections (the C5-6 defect in the lateral film is obscured by the shoulder shadows).

FIG. 2. *F. C.* Nearly complete subarachnoid block in the anteroposterior projection at the C4-5 and C5-6 disk levels. Note that the lateral view fails to reveal the true size of the lesion. There is minimal abnormality seen on the plain cervical spine film.

one level, and in only two patients were single defects seen. Thus midline filling defects were demonstrated at two levels in five patients, at three levels in 19 patients, and at four levels in six patients.

Midline filling defects at C 5-6 were observed on 31 myelograms, at the C 6-7

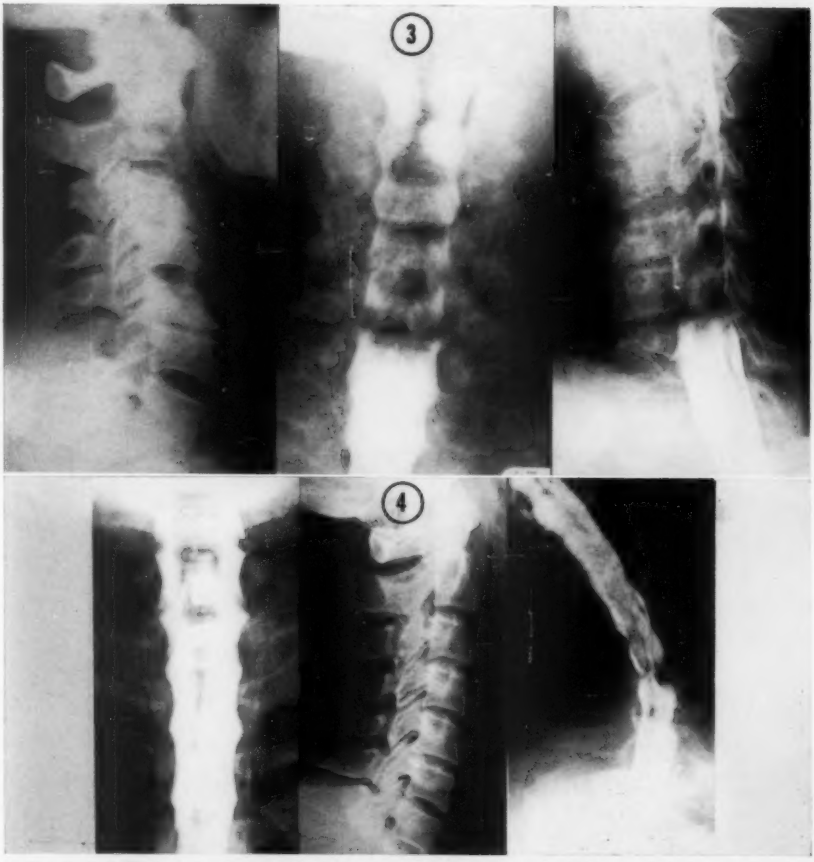


FIG. 3. *L. I.* High grade subarachnoid block at four disk levels, two of which are relatively normal and two almost obliterated as seen in the plain x-ray film.
FIG. 4. *O. P.* Note close correlation between the size and location of the posterior osteophyte at C5-6 and the associated myelographic defect. In this instance the lateral film gave a more accurate picture of the lesion disclosed at operation than did the anteroposterior projection.

level 27 times, at the C 4-5 level 22 times, at the C 3-4 level nine times, and at the C7-T1 level on four occasions. There was no correlation between the size of the myelographic defect demonstrated and the frequency with which protrusions occurred at any specific level. It was interesting to observe that in no instance was a large protrusion at the C7-T1 level demonstrated radiographically.

The severity of the lesions demonstrated varied from minimal central protrusion of the intervertebral disk at one or two levels without lateral extension (figure 1), to nearly complete subarach-

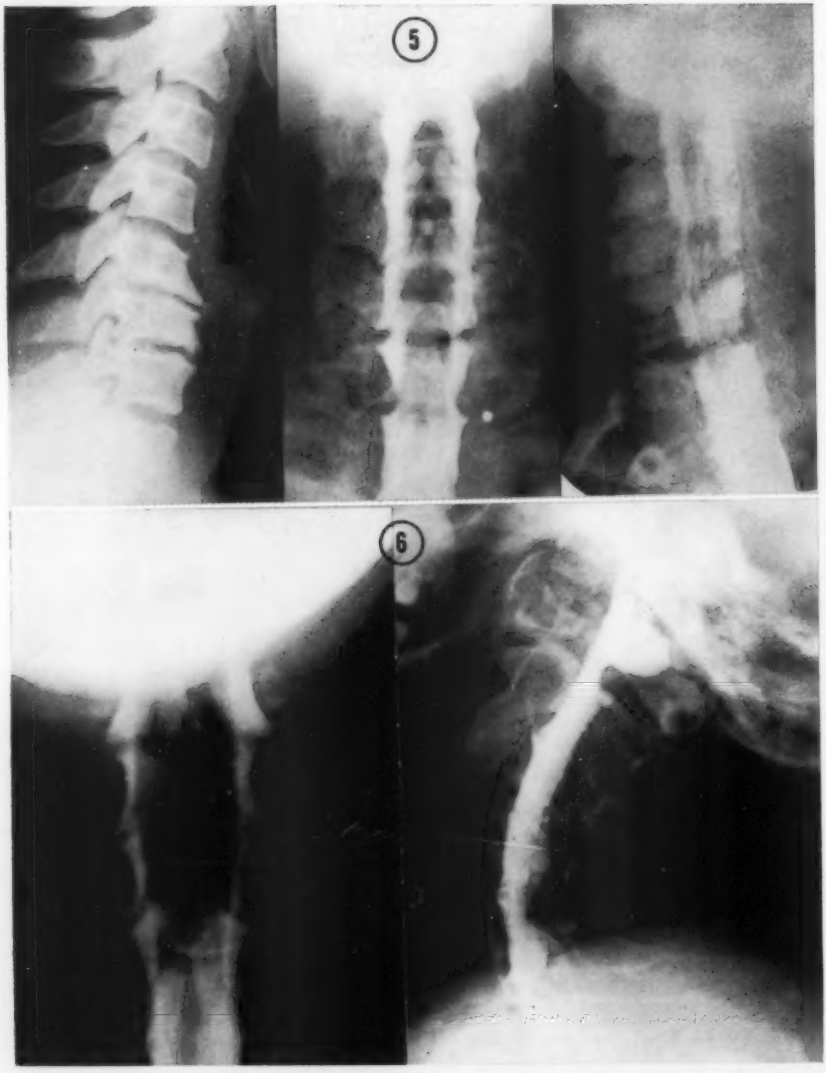


FIG. 5. *O. D.* Filling defects of moderate size at the C3-4, C4-5, C5-6, and C6-7 disk levels, with marked bony changes on the plain films at C5-6 and C6-7.

FIG. 6. *J. B.* Myelogram simulating the appearance of an expanding intramedullary lesion. The marked narrowing of the spinal canal by the multiple disk ridges allows Pantopaque to pass by only in the lateral gutters and thus the ridges fail to show up on either the lateral or anteroposterior myelographic film.

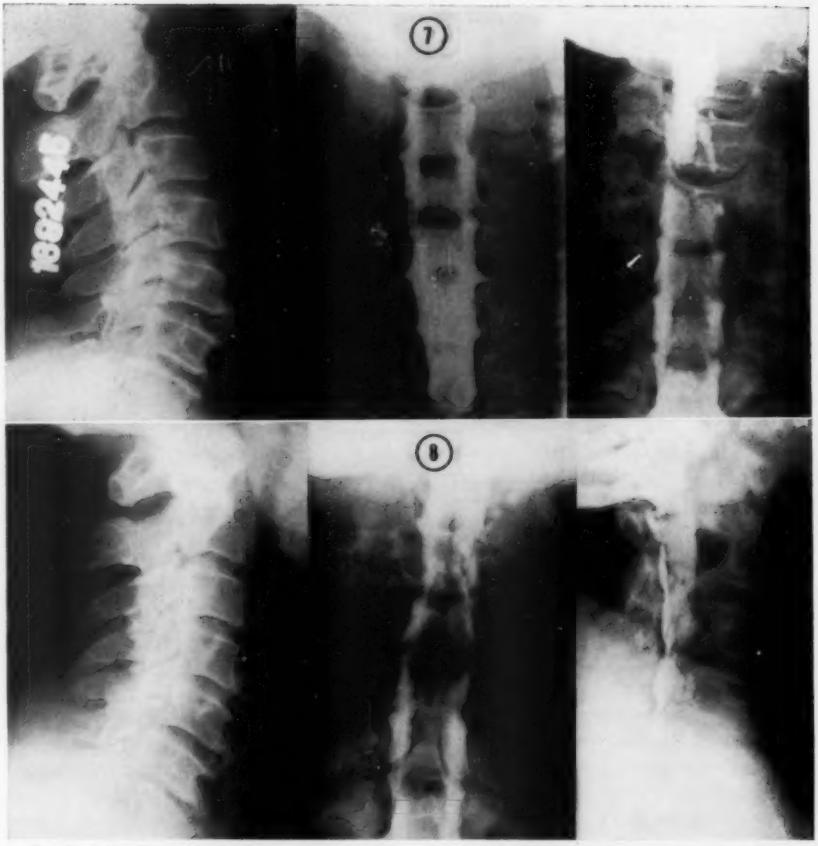


FIG. 7. *R. R.* Cervical spine and myelogram films made in 1949 showing moderate sized midline filling defects at the C4-5, C5-6, and C6-7 disk levels.

FIG. 8. *R. R.* Repeated examination in 1953 of same patient as in figure 7. Note the increase in size of the filling defects with little change in bony abnormalities.

noid block (figure 2). High grade obstruction of the subarachnoid space at several levels was frequently observed (figure 3). Occasionally the bony spurs predicted accurately the size of the filling defect (figure 4), but more often the correlation was poor. Large filling defects were associated with minimal abnormality in the plain roentgenograms (figure 2) and severe bony changes were often associated with much smaller filling defects (figure 5).

In some instances the filling defects were equally well visualized in both the anteroposterior and lateral projections (figure 1). If the lateral gutters were shallow the filling defect was more pronounced in the lateral films (figure 4).

If the lateral gutters were deep and well filled, the filling defect was often minimal or absent on the lateral projection and appeared mainly as a midline radiolucent area in the anteroposterior projection (figure 2). There was no correlation between the presence or degree of cervical intervertebral disk protrusion with disk protrusions either in the lumbar or thoracic spine.

In two patients the myelographic findings were of sufficient interest to warrant further description. The first of these two patients was a 37 year old white male whose predominant symptom was radicular arm pain. The myelogram (figure 6) revealed widening of the spinal cord shadow over several of the lower cervical segments and simulated the radiographic appearance of an expanding intramedullary lesion. At operation multiple midline cervical disk protrusions were demonstrated at the appropriate levels and the spinal cord was flattened and widened over the protrusions. Aspiration of the spinal cord failed to reveal a syrinx and there was no evidence of an intramedullary lesion. After section of the dentate ligaments the cord moved backward and regained its normal size and shape.

The second patient was a 59 year old white male who gave a history of longstanding progressive ataxia and weakness of both lower extremities. In 1949 the patient had had a myelogram performed at another hospital (figure 7). Because of the progression of symptoms the myelogram was repeated at this clinic in 1953 (figure 8). The increase in size of the myelographic defect correlated well with the progression of the patient's signs and symptoms during the four year interval.

OPERATIVE TREATMENT AND COMPLICATIONS

The surgical procedure in each patient consisted of a moderately wide bilateral cervical laminectomy (usually five or six laminae in order to extend the removal to include one lamina above and below the humps) and section of the dentate ligaments bilaterally throughout the limits of the operative exposure. The operations were carried out in the sitting position. In the earlier cases the subarachnoid space was opened widely. In later cases the arachnoid was not opened and the dentate attachments were cut in the subdural space. This markedly reduced the incidence of complications listed below. In all but three patients the dura was not closed in order to obtain maximal decompression of the cervical spinal cord. Extradural removal of a single large soft or hard midline protrusion in addition to the laminectomy was performed in six patients.

Following operation four patients had transient episodes of marked disorientation, and one of these four patients developed a frank psychosis. In each of the four patients the disorientation cleared completely within four weeks after operation. One patient developed a deep wound infection which responded to drainage and antibiotic therapy. One patient developed a transient paraplegia immediately after operation but regained all function within three weeks. One patient, who had a mild paraparesis before operation, exhibited transient increase in the weakness of the lower extremities. One patient developed massive hematemesis from a previously silent duodenal ulcer on the second day after operation. The gastrointestinal hemorrhage ceased in five days and did not present any further problem.

One patient expired suddenly six days after operation. Necropsy revealed massive hemorrhage into the right lateral ventricle, right basal ganglia, and into the brainstem bilaterally. A second patient developed a superficial wound infection followed by dehiscence of the laminectomy wound. Following secondary closure of the wound, there was persistent leakage of cerebrospinal fluid from the incision. Signs of brainstem damage appeared shortly before his death four months after the first operation. Autopsy disclosed a severe adhesive arachnoiditis involving the entire spinal cord, the brainstem, and base of the brain. If this complication can be charged to the myelogram, it constitutes the only serious complication encountered in our series of over 700 myelograms.

FOLLOW-UP RESULTS

The results of the follow-up examinations are presented in two groups based on length of time since operation.

Two to Five Year Follow-up

Six of the 32 patients have been followed for two to five years. Two of the six patients had had limited laminectomies with intradural section of dentate ligaments bilaterally in association with removal of a single, large, bony hard, midline protrusion. One of these two patients is much improved. Motor weakness, ataxia, extensor plantar responses, and atrophy of small muscles of hands bilaterally have disappeared. The other patient did not improve and died at home of other causes 24 months after operation. The remaining four patients had extensive cervical laminectomy and bilateral section of the dentate ligaments alone. Of these four, two are unchanged and two are objectively improved.

Eight to 24 Month Follow-up

Twenty-one of the 32 patients have been followed for a period of eight to 24 months. Of these patients, two had removal of a single intervertebral disk protrusion as well as a limited laminectomy and bilateral section of one or two pairs of dentate ligaments. One of these two patients improved; the other developed progression of neurologic signs and symptoms including bulbar palsy and died, presenting finally the typical picture and course of amyotrophic lateral sclerosis.

In the remaining 19 patients extensive laminectomies and section of the dentate ligaments were carried out. Six patients have improved and 12 patients have had no change in either their symptoms or their neurologic deficit. One patient has had progression of symptoms and is much worse 13 months after operation.

The remaining five patients have been lost for follow-up purposes.

The over-all results reveal that of the 27 patients who have been followed from eight to 56 months after operation, ten patients (37 per cent) have improved and 14 patients (52 per cent) have not been improved. However, in these latter 14 patients, the progression of symptoms, rapid in some and slow in others, which was observed before operation has ceased and their condition has remained stationary to date. Two of the 27 have become progressively worse, and in one it has become quite evident that the correct diagnosis was amyotrophic lateral sclerosis and the disk protrusions, which in this instance had produced a partial subarachnoid block, were not responsible for the degenerative process. The remaining patient did not improve and died at home of other causes 24 months later.

DISCUSSION

Chronic compression of the cervical spinal cord due to longstanding midline protrusion of one or more intervertebral disks may frequently be difficult to diagnose due to similarity in the clinical picture with such diseases as primary lateral sclerosis, multiple sclerosis, amyotrophic lateral sclerosis, and other primary degenerative diseases of the spinal cord.

The symptoms most frequently encountered in this series were: 1) progressive weakness of one or both lower extremities; 2) disturbances of gait; 3) unremitting paresthesia in one or both upper extremities with or without involvement of the trunk or lower extremities; and 4) varying degrees of weakness of the upper extremities. In general the patients stated that the symptoms had become progressively worse but there was considerable variability in the rapidity of the course of the illness. The symptoms were present for less than six months in six patients, for six to 12 months in eight patients, and for two to five years in 16 patients. The remaining two patients had symptoms which began eight and 12 years before entry into the hospital. Motor weakness and disturbances of gait were the presenting complaints of 20 of the 32 patients, whereas sensory disturbance was the presenting complaint of the remaining 12 patients. There were no symptoms referable to dysfunction of the cranial nerves or brainstem. The signs of spinal cord damage were primarily those of dysfunction of the corticospinal tracts and the posterior columns. Hyperreflexia, extensor plantar responses, ataxia, spasticity, and incoordination were commonly encountered.

It has become our custom to consider the possibility of midline cervical disk protrusions in all patients with evidence of chronic spinal cord disease in whom a definite etiologic factor such as syphilis, pernicious anemia, poorly controlled diabetes mellitus, and so on, is absent, and in all patients suspected of having multiple sclerosis who do not have definite evidence of cranial nerve dysfunction or clear-cut typical remissions of symptoms and signs. The syndromes often classified as progressive spinal multiple sclerosis and primary lateral sclerosis particularly merit myelographic examination, in our opinion. It should be noted that examination of the cerebrospinal fluid did not substantially aid in establishing a diagnosis, since in nearly half (47 per cent) of the patients in this series examinations of the cerebrospinal fluid were within normal limits.

Radiologic examination of the cervical spine usually showed definite bony abnormalities, alterations in the curvature of the cervical spine, narrowing of the intervertebral spaces, and presence of osteophytes. Two or more of these abnormalities were demonstrated in each of the 32 patients. These alterations, however, do not prove that the spinal cord damage is due to pressure of midline disk protrusions since in older age groups they are frequently encountered in the absence of symptoms or signs of spinal cord compression.

The role of myelography in all cases where compression of the spinal cord is suspected has been emphasized by Kristoff and Odom,[25] Epstein and Davidoff,[20] and Rosner.[34] Other authors[6, 11,13,47] have seriously questioned the value of myelography. It is our opinion that neither the diagnosis nor the exclusion of chronic compression of the cervical spinal cord due to lesions of the

intervertebral disks can be established without careful and complete myelographic examination with an adequate quantity of contrast media. This has been emphasized also by Bradford and Spurling.[8, pp. 133-4.]

It is well known, however, that when routine cervical myelographic films are made at the time of myelography for lesions elsewhere, for example for lumbar disk protrusions, midline cervical disk elevations are not infrequently visualized, particularly in older patients, without any evidence of spinal cord damage. Some additional factor must therefore be postulated in those patients who develop cord damage. That such degeneration does occur has been amply demonstrated by the studies of Mair and Druckman,[26] Spillane and Floyd,[38] Bedford and co-workers,[7] and Brain and his associates.[10] This additional factor could conceivably be the duration of the bulge; or the relative size of the hump, spinal cord, and spinal canal; or the amount of movement of the cord over the ridges;[39] or the role of the dentate ligament in holding the spinal cord against the space-taking lesion, as described by Abrahamson and Grossman[1] and emphasized by Kahn.[24] Kahn felt that the strong attachments of the dentate ligaments may prevent equal distribution of pressure in the presence of anterior spinal cord compression and result in the clinical syndrome described. He also suggested that there might be an increase in the size and strength of the dentate ligaments and their attachments in longstanding chronic cord compression. Although it is a speculation, it seems plausible to us that variations in length and site of attachment of the dentate ligaments may be of importance in determining whether the midline disk elevations are associated with spinal cord damage or not.

Mair and Druckman[26] correlated the clinical features observed in four patients who had protrusions of cervical intervertebral disks with the findings in the spinal cord at necropsy. Their studies revealed lesions similar to those produced by ischemia of the spinal cord, involving principally the anterior horns, the lateral horns, and the anterior part of the dorsal columns, coinciding with the area supplied by the anterior spinal artery except for the anterior white columns which were spared. They concluded that compression of the anterior spinal artery by the ventral elevations was responsible for the lesions and that the sparing of the ventral white columns was due to the fact that the proximal branches of the artery were shorter and therefore subjected to less obliterative effect. It is of interest, as mentioned in this article, that Tureen, on theoretical grounds, had made a similar suggestion in 1937.[45, pp. 428-429.] Kahn's theory of the mechanical factors seemed to Mair and Druckman untenable in the light of their histologic studies. Abrahamson and Grossman[1] and Brain[9] have also emphasized the importance of vascular factors in producing the spinal cord damage. It seems plausible to us that the dentate ligaments may play a role in bringing about chronic compression of the anterior spinal artery by the ridges and thus the above two theories are not necessarily mutually exclusive.

We were particularly interested in the follow-up results in this series, since the proper surgical treatment of this lesion is not agreed upon. Although single soft midline disk protrusions can be removed from in front of the cord without undue risk and with good recovery of function, attempts at removal of midline calcified

or bony ventral ridges have proved to be hazardous in the hands of most neurosurgeons. The multiplicity of these lesions and their tendency to occur in older patients discourages attempts at removal, although Allen[6] has described a technic which in his hands has given excellent results. The conservative surgical procedure carried out in most of these patients was decided upon as the safest procedure that offered hope of arresting the progression of cord damage. Section of the dentate attachments, allowing the cord to ride backward away from the ventral ridges, seems to us more important than the removal of the laminae, since few of these patients showed any evidence of significant block of the subarachnoid pathway.

The follow-up results obtained to date in this series of patients are encouraging and are similar to those reported by Brain and his associates.[10] Although none of the patients have been cured in the sense that all the symptoms have disappeared since operation, there was definite improvement in ten patients (37 per cent of those followed and 31 per cent of the total group). Fifteen patients (56 per cent of those followed and 47 per cent of the total group) who have not exhibited improvement since operation have had no increase in neurologic deficit. It must be emphasized that many of these latter patients had exhibited rapidly increasing signs and symptoms of spinal cord dysfunction.

We wish to put these results on record in the hope that comparison with results of other procedures will lead to more effective therapy and agreement on the procedure of choice. For example, it seems desirable to determine whether addition of fusion to the decompression would be desirable. The theoretically ideal procedure of removal of the humps may become feasible with improved instruments and experience.

It is our belief that patients who exhibit the signs and symptoms of chronic dysfunction of the spinal cord without evidence of involvement of cranial nerves or bulb should be suspected of harboring midline cervical intervertebral disk protrusions. Myelography should be performed to confirm or rule out the presence of this lesion. In those instances where midline protrusions are detected, operation should be seriously considered. Occasionally it will be extremely difficult to differentiate the condition from the early stages of amyotrophic lateral sclerosis or other primary degenerative lesions of the spinal cord. It is our opinion that where such differentiation is impossible it may be advisable to operate in the hope that the disk protrusions are the cause of the spinal cord dysfunction. Occasionally a patient will ultimately be found to have primary degeneration of the spinal cord and the course will not be altered by the operation, but we believe many patients will be benefited by arrest of progression of disability.

Since the pathologic changes produced by long continued local pressure on the ventral aspect of the spinal cord are often irreversible, early diagnosis and treatment are particularly important. Except in early cases the practical criterion of success should be arrest of progression of the signs and symptoms of spinal cord dysfunction.

SUMMARY

1. A survey is presented of a series of 32 consecutive patients operated on for the syndrome of chronic spinal cord compression due to longstanding mid-

line cervical disk protrusion or ridges ("cervical spondylosis" or "osteoarthritis").

2. The principal symptom was weakness of the extremities which occurred in each of the 32 patients. Paresthesias of varying severity and extent were noted by 21 (69 per cent) of the patients. Ataxia was sometimes the principal complaint and was reported by 18 (56 per cent of the patients). Fifteen patients (47 per cent) presented minor complaints of pain, usually nonspecific in type, located in the neck, suboccipital region, shoulder, or arm.

3. The principal neurologic findings were upper motor neuron type of paresis of the legs with varying degrees of spasticity (present in 23 or 72 per cent of the patients) and ataxia (present in 18 or 56 per cent of the patients).

4. The cerebrospinal fluid protein was normal in 15 patients, ranged from 50 to 89 mg. per cent in 12 patients, and from 90 to 134 mg. per cent in three patients.

5. The evidences of disk degeneration and repair seen on the plain cervical spine films frequently could not be correlated with the myelographic evidence of encroachment on the spinal canal.

6. Myelographic evidence, using the full column technic, accurately predicted the findings at operation. Protrusions were multiple in 30 of the 32 patients. In most instances the anteroposterior projection was most valuable, but in some the lateral projection was more reliable and valuable.

7. The basic operative procedure used was a posterior decompression, removing a sufficient number of laminae so as to include at least one lamina below the lowest ridge and one lamina above the uppermost ridge, and section of the dentate ligaments throughout the exposure.

8. Twenty-seven of the 32 patients were followed with repeated neurologic examinations for periods ranging from eight months to five years. Ten patients (37 per cent of those followed, or 31 per cent of the total group) were objectively improved. Fifteen patients (56 per cent of those followed or 47 per cent of the total group) have had no increase in neurologic deficit and their progressive spinal cord lesion apparently has been arrested to date.

CONCLUSIONS

1. It seems probable that a significant proportion of patients that have been classified in the past under diagnoses such as primary lateral sclerosis, progressive spinal multiple sclerosis, chronic degeneration of the spinal cord due to arteriosclerosis, atypical amyotrophic lateral sclerosis, and so on may be suffering from a low grade mechanical compression of the ventral aspect of the spinal cord due to midline cervical disk protrusions or ridges (cervical "spondylosis" or "osteoarthritis").

2. The follow-up results in this series of patients suggest that a simple posterior decompression is a valuable therapeutic procedure. Comparison of these results with follow-up studies after other types of surgical procedures may lead to more effective therapy.

3. Since the changes in the spinal cord produced by these lesions are often irreversible, early diagnosis and treatment is particularly important. The practical criterion of success should be arrest of progression. Improvement should be expected only in early cases.

REFERENCES

1. Abrahamson, I., and Grossman, M.: Tumors of the upper cervical cord, Tr. Am. Neurol. A. 47: 149, 1921.
2. Adson, A. W., and Ott, W. O.: Results of removal of tumours of the spinal cord, Arch. Neurol. & Psychiat. 8:520, 1922.
3. Adson, A. W.: Diagnosis and treatment of tumors of the spinal cord, Northwest Med. 24:309, 1925.
4. Alajouanine, T., and Thurel, R.: Hernie discale de la region cervicale, Rev. neurol. 78:53, 1946.
5. Alajouanine, T., and Thurel, R.: Hernie discale de la region cervicale: quadriplegie cerebello-spasmodique simulant la sclerose en plaques, Rev. neurol. 79:765, 1947.
6. Allen, K. L.: Neuropathies caused by bony spurs in the cervical spine with reference to surgical treatment, J. Neurol., Neurosurg. & Psychiat. 15: 20, 1952.
7. Bedford, P. D., Bosanquet, F. D., and Russell, W. R.: Degeneration of the spinal cord associated with cervical spondylosis, Lancet 2:55, 1952.
8. Bradford, F. K., and Spurling, R. G.: The Intervertebral Disk, Springfield, Ill., Charles C Thomas, publisher, 1945, 192 pp. (pp. 133-4).
9. Brain, W. R., and Bull, J. W. D.: Discussion on rupture of the intervertebral disk in the cervical region, Proc. Roy. Soc. Med. 41:509, 1948.
10. Brain, W. R., Northfield, D., and Wilkinson, M.: The neurologic manifestations of cervical spondylosis, Brain 75:187, 1952.
11. Browder, E. J., and Watson, R.: Lesions of the cervical intervertebral disk: Clinicopathologic study of twenty-two cases, New York State J. Med. 45: 730, 1945.
12. Bucy, P. C., and Chenault, H.: Compression of seventh cervical nerve root by herniation of an intervertebral disk, J.A.M.A. 126:26, 1944.
13. Bucy, P. C., Heimburger, R. F., and Oberhill, H. R.: Compression of the cervical cord by herniated intervertebral disks, J. Neurosurg. 5:471, 1948.
14. Dandy, W. E.: Loose cartilage from intervertebral disk simulating tumor of the cord, Arch. Surg. 19: 660, 1929.
15. Dandy, W. E.: Serious complications of ruptured intervertebral disks, J.A.M.A. 119:474, 1942.
16. Den Hartog Jager, W. A., and Moffie, D.: Medullary syndromes simulating multiple sclerosis, amyotrophic lateral sclerosis, subacute combined degeneration of the cord and syringomyelia, caused by herniation of intervertebral cervical disk, Folia psychiat. neurol. et neurochir. neerl. 52:137, 1949.
17. Dexler, H.: Beitrage zur Pathologie und pathologischen Anatomie der Compressionsmyelitis des Hundes, Oesterreich. Ztschr. f. Wissensch. Veterinark 7:1, 1895-96.
18. Elsberg, C. A.: Extradural spinal tumors; primary, secondary, metastatic, Surg., Gynec. & Obst. 46:1, 1928.
19. Elsberg, C. A.: The extradural ventral chondromas (ecchondrosis): Their favorite sites, the spinal cord and root symptoms they produce and surgical treatment, Bull. Neurol. Inst. N. Y. 1:350, 1931.
20. Epstein, J. A., and Davidoff, L. M.: Chronic hypertrophic spondylosis of the cervical spine with compression of the spinal cord and nerve roots, Surg., Gynec. & Obst. 93:27, 1951.
21. Frykholm, H.: Lower cervical vertebrae and intervertebral disks: Surgical anatomy and pathology, Acta chir. scandinav. 101:345, 1951.
22. Gehuchten, P. Van: Diagnosis and treatment of spinal cord compression caused by cervical hernia, Folia psychiat. neurol. et neurochir. neerl. 56:468, 1953.
23. Hawk, W. A.: Spinal compression caused by ecchondrosis of the intervertebral fibrocartilage, with a review of the recent literature, Brain 59: 204, 1936.
24. Kahn, E. A.: The role of the dentate ligaments in spinal cord compression and the syndrome of lateral sclerosis, J. Neurosurg. 4:191, 1947.
25. Kristoff, F. V., and Odom, G. L.: Ruptured intervertebral disk in the cervical region, Arch. Surg. 54:287, 1947.
26. Maim, W. G. T., and Druckman, R.: The pathology of spinal cord lesions and their relation to the clinical features in protrusion of cervical intervertebral disks: A report of four cases, Brain 76: 70, 1953.
27. Meyer, B. P., and Fine, B. D.: Atypical syndromes produced by extramedullary tumor of cervical portion of spinal cord, Arch. Neurol. & Psychiat. 61:262, 1949.
28. Mixter, W. J., and Barr, J. A.: Rupture of the intervertebral disk with involvement of the spinal canal, New England J. Med. 211:210, 1934.
29. Mixter, W. J., and Ayer, J. D.: Herniation or rupture of the intervertebral disk into the spinal canal, New England J. Med. 213:385, 1935.
30. Muller, R.: Protrusion of cervical intervertebral disks with lesion of the spinal cord, Acta med. scandinav. 139:85, 1951.
31. Olson, S., and Hansen, H.: Cervical disk protrusions in the dog, Am. J. Vet. Res. 121:361, 1952.
32. Peet, M. M., and Echols, D. H.: Herniation of the nucleus pulposis: A cause of compression of the spinal cord, Arch. Neurol. & Psychiat. 32: 923, 1934.
33. Poppen, J. L., and Fountain, E. M.: Protruded cervical intervertebral disk; experiences with 37 cases, Surg. Clin. North America 31:891, 1951.
34. Rosner, S. J.: Neurosurgical observations in the multiple sclerosis syndrome, J. Nerv. & Ment. Dis. 114:511, 1951.
35. Schlesinger, E. B., and Wood, E. H.: Factors in the pathogenesis and diagnosis of spastic paraparesis due to cervical cord compression, the so-called pseudo multiple sclerosis, Tr. Am. Neurol. Assoc. 77:140, 1952.
36. Scoville, W. B., Whitcomb, B. B., and McLaurin, R.: The cervical ruptured disk: Report of 115 operative cases. Trans. Am. Neurol. A. 76:222, 1951.
37. Sheldon, H., and Pudenz, R.: Ruptured cervical intervertebral disks, California Med. 72:156, 1950.
38. Spillane, J. D., and Lloyd, G. H. T.: Spastic paraplegia in late adult life with degeneration and

protrusion of cervical disks, Lancet 2:653, 1951.
39. Spillane, J. D., and Lloyd, G. H. T.: The diagnosis of lesions of the spinal cord in association with "osteoarthritic" disease of the cervical spine, Brain 75:177, 1952.
40. Spurling, R. G., and Scoville, W. B.: Lateral rupture of the cervical intervertebral disks, Surg., Gynec. & Obst. 78:350, 1954.
41. Stookey, B.: Compression of the spinal cord due to ventral extradural cervical chondromas, Arch. Neurol. & Psychiat. 20:275, 1928.
42. Stookey, B.: Compression of the spinal cord and nerve roots by herniation of the nucleus pulposis in the cervical region, Arch. Surg. 40:417, 1940.
43. Strully, K. G., Gross, G. W., Schwartzman, J., and von Storch, T. J. C.: Progressive spinal cord disease: Syndromes associated with herniation of cervical intervertebral disks, J.A.M.A. 146:10, 1951.
44. Taylor, J., and Collier, J.: The occurrence of optic neuritis in lesions of the spinal cord: Injury, tumor, myelitis (an account of twelve cases and one autopsy), Brain 24:532, 1901.
45. Tureen, L. L.: Circulation of the spinal cord and the effect of vascular occlusion, A. Res. Nerv. & Ment. Dis., Proc. 18:394, 1937.
46. Walker, A. E., Moore, W. W., and Simpson, J. R.: Diagnosis and surgical treatment of cervical disk lesions, J. Internat. Coll. Surgeons 15:411, 1951.
47. Whiteleather, J. E., Semmes, R. E., and Murphy, F.: The roentgenographic signs of herniation of the cervical intervertebral disk, Radiology 46:213, 1946.

CORRECTION

On pages 402 and 403 of the June issue of NEUROLOGY (5:394-406, 1955), an error in the translation from the original Russian occurs in the paper "S. S. Korsakoff's Psychic Disorder in Conjunction with Peripheral Neuritis," by Maurice Victor, M.D. and Paul I. Yakovlev, M.D. The correct translation of the entire paragraph follows:

By the end of October, in addition to the signs of parametritis and pyemia, symptoms of involvement of the nervous system appeared. The patient began to have delirium, she spoke incoherently, and at times was agitated. The character of her psychosis was peculiar. According to the statement of the attending physician, at times she spoke entirely rationally, gave a correct account of everything, and did not confuse anything, so that it was difficult to notice any psychic abnormality; but then, suddenly confusion would begin, delirium would develop, the patient would become restless and beset with fear, she would hallucinate, would see dogs and monsters, and would attempt to jump out of bed and to tear off her dressings. These attacks would usually occur towards evening when the patient would generally become more agitated and alarmed; she would constantly summon people, would become tormented by fear, and then an attack of intense anxiety with illusions and hallucinations would develop. At first the patient had difficulty in falling asleep and frequently awoke. Awakening, she would become restless, again would summon people, shout, and then again would fall asleep for a short while only to wake up in the same state of anguish. So it continued throughout the whole of November. In December some improvement began: the attacks of violence diminished, she became quieter and much more rational. But, with this improvement the enfeeblement of memory became all the more noticeable. The patient would forget who had visited her; she would forget what she herself had said and so she would constantly repeat one and the same thing, tell the same stories time and again, and ask the same questions. Her sleep continued to be irregular. At times there was vomiting; at times the patient complained of pain in the sacral region; for a time she could hear almost nothing and lost her sense of smell. I saw the patient on December 30, 1888 in consultation with her attending physician, Dr. M. D. Lebedev, and found her in the following state:

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *D. Denny-Brown, M.D. and J. M. Foley, M.D.*

CASE REPORT

A 23 year old white married woman was admitted to the obstetrics service on October 5, 1954 with a chief complaint of generalized abdominal pain for four months. She had been having noncramping, generalized abdominal pain, more in the right upper quadrant, without any change in appetite or bowel habits. She claimed to be eight months pregnant; otherwise the patient's ability to give a history was negligible.

Her mother said that the patient was in apparent excellent mental and physical health the day before admission, but didn't see her walk, however. The patient was in bed with a sheet pulled up over her abdomen, since the mother was not supposed to know she was pregnant.

In 1947 she had attempted suicide with an overdose of phenobarbital. In November 1949 she was hospitalized for sharp abdominal pain, diagnosed as five month pregnancy with threatened miscarriage. She delivered a full term healthy baby in April 1950, and signed out against advice in three days. Two months later she was admitted to the medical service for fatigue, anorexia, abdominal cramps, and jaundice. There was no history of transfusions, but she had received four penicillin injections in the puerperium in April 1950. She signed out against advice on the thirteenth hospital day. The diagnosis was "acute infectious hepatitis, viral etiology."

In September 1951 she was admitted to the surgical service for abdominal pain, anorexia, and diarrhea. The diagnosis was "possible neurasthenia." Again in December 1953 she was hospitalized for nausea, vomiting, and anorexia of four weeks' duration. Cephalin flocculation was 2+, icteric index 24, bromsulphalein 8 per cent. Graham-Cole series was negative.

At this most recent admission, physical examination showed temperature 99.6°, pulse 112 (regular), respirations 24, and blood pressure 100/70. The patient was lethargic and flushed, but in no acute pain. Fine basal crepitant rales were heard bilaterally, as well as grade 1 apical systolic murmur. The aortic second sound was greater than the pulmonic. The uterus was midway between the umbilicus and symphysis. Slight costovertebral angle tenderness was noted on the right side, as well as tenderness in both upper quadrants. The neurologic examination was negative.

On admission to the ward, the patient was pale, with skin turgor poor. She was hyperventilating, and responded poorly to questions. Fetal heart sounds were heard in the right lower quadrant. The vertex was presenting and floating.

Laboratory studies gave the following values: Urine—dark yellow; pH 5.5; specific gravity 1.008; albumin 10 mg. per cent; no sugar; no bile; sediment negative. Hematocrit—45 per cent. White cell count—8750. Nonprotein nitrogen—31 mg. per cent. CO_2 combining power—43 per cent; chlorides—111mEq.

Course: On the second hospital day, the patient was "clinically well hydrated after intravenous therapy, drowsy, poorly oriented, diplopic." The psychiatric consultant noted that she was "severely depressed and retarded . . . .

From the neurological unit and the Mallory Institute of Pathology, Boston City Hospital, and the department of neurology, Harvard Medical School, Boston.

drowsy . . . . sighs constantly." On the third hospital day she delivered a 4 lb. premature infant.

On the fourth hospital day she was afebrile and sleepy. Although nystagmus had not been mentioned previously the record states "nystagmus still present."

On the fifth hospital day she was "slightly confused – unmanageable – clinically dehydrated." During the day she spiked a temperature to 104°, began to cough, and developed copious tracheobronchial secretions. Urinalysis at this point showed a specific gravity of 1.020, acid reaction, albumin 35 mg. per cent, acetone 2+, sugar 3+ (on intravenous glucose) and 13,000 white blood cells; CO_2 combining power was 35 per cent, nonprotein nitrogen 37, and chlorides 98. She was started on penicillin after blood cultures were taken. A medical consultant found right lower lobe atelectasis and bronchopneumonia.

On the sixth hospital day she was seen by the neurologic consultant, part of whose notes are as follows: "Has never walked since being here; has been on floor several times and resists fairly strongly when being put back. Has been confused, at times uncertain where she was. She denies diplopia now but in first few days told doctors she had diplopia. Knows name, says this is Boston City Hospital, says she is 19, that this is 1953. Denies drugs in past. Not hallucinating. Can't do formal memory testing.

"Disks slightly blurred on margins, not elevated. Fundi negative. Pupils normal. Cannot or will not move eyes more than a little medially or laterally, but upward gaze and downward gaze has fair movement – Facial movements probably normal – Hears – Gags, swallows – Good grip but weakness on repetitive movement. Moves legs but only on painful stimulus and not well. No ataxia – all deep reflexes absent, plantars flexor – feels pin all over."

A lumbar puncture was done at this time. The initial pressure was 145. There was one red cell and one lymphocyte. The Pandy was negative. She did not respond to a test dose of neostigmine.

A few hours later she was cyanotic and breathed stertorously. She died in the evening of the sixth hospital day.

CLINICAL DISCUSSION

DR. DENNY-BROWN: When the chief complaint is one of pain, one naturally proceeds to seek as close definition of its type, situation, frequency, and precipitating factors as possible. In this case, owing to the state of the patient and to her having concealed her condition from her mother, such information was greatly restricted. But we do know that these were not cramps or colic and that they were not the shooting or girdle sensations that are common in spinal disease. The patient added that she had been unable to take fluids or food by mouth, and I think we may assume that there had been vomiting for an indefinite period, possibly for four months.

The past medical history of attempted suicide with phenobarbital at the age of 16 years strongly suggests an overemotional personality. The episode of hepatitis four years earlier raises the question of possible recurrent hepatitis in September 1951, December 1953, and in the present admission.

On admission it was noted that besides the frequency and tender abdomen there was lethargy and "poor response to questions" but no neurologic signs. We would like to know more of the nature of response to questions, but perhaps could not expect a more detailed record of this on an emergency admission to an obstetric ward. At all events the immediate laboratory work revealed no anemia, no evidence of infection, and no gross evidence of hepatic, renal, or other metabolic disease. Dehydration was evidently obvious, for on the second hospital day it was noted that she was well hydrated after intravenous therapy. In addition drowsiness, poor orientation, and diplopia are mentioned. Disorientation at once indicates that there was an impairment of cerebral function, a possibility that had been raised by the poor response to questions the previous day. Disorientation is a positive neurologic sign, as unequivocal as an extensor plantar response in indicating that brain function is damaged, and that there was more here than pregnancy and neurosis. This history of overdosage of barbiturates seven years earlier no doubt raised the question of similar overdosage to account for the severe drow-

siness and disorientation, and a psychiatric consultant on the second day noted severe depression and retardation but was evidently unwilling to reach any particular conclusion as to the cause. The diplopia no doubt troubled him, as it would me.

After delivery of the premature infant on the third day the drowsy state continued to the fourth and fifth days. Persisting nystagmus might still have suggested barbiturate intoxication, except that there had been no improvement in the mental condition and no proof of ingestion. The bronchopneumonia on the fifth and sixth days was associated with appropriate leukocytosis but no other remarkable change, except that glycosuria with acetone appeared and was attributed to intravenous glucose.

A neurologic consultant saw the patient for the first time on the sixth day. He noted the mental confusion and disorientation in place and time, without hallucinations, with complete paralysis of lateral movements of the eyes, slightly blurred disks, and absent tendon reflexes. Weakness of the limbs was evident, and though no ataxia was demonstrable in the upper limbs he evidently raised a question whether the inability to use the lower limbs was preceded by ataxic gait. The uncooperative state of the patient enabled him to say only that there was a response to pinprick in all parts examined. A lumbar puncture gave no additional information, except that the blurring of the optic disks was not associated with high lumbar puncture pressure. The eye signs and general weakness evidently prompted a test injection of neostigmine. It is not clear from the record given whether death was the consequence of respiratory or cardiac failure, but the rapid development of cyanosis without respiratory irregularity strongly suggests the latter.

In this tragic series of events the neurologic sequence indicates impairment of brain function of a diffuse kind, associated with possible ataxic weakness of the lower limbs and nystagmus, and after a few days, with progressive lateral rectus paralysis and increasing disorientation. There was ultimate loss of tendon reflexes and probable cardiac failure associated with terminal bronchopneumonia. Of the various possibilities that come to mind the first would be that of toxic encephalopathy possibly from barbiturates. We have already indicated that though nystagmus is common in such states, lateral rectus paralysis, once it appeared, clearly indicated some other pathology. Though there had been episodes of abdominal pain in the past and at the beginning of the present illness, these were accounted for by pregnancy and hepatitis on each occasion and were not of the colicky type seen in porphyria. Nor are ocular palsies a feature of porphyria.

The neurologic signs are of a diffuse process, and I would therefore not seriously consider focal cerebral disease except possibly cerebral thrombophlebitis. In that condition, which in any case occurs as a metastatic complication of pelvic phlebitis in the puerperium, convulsions and unilateral postictal limb weakness might be expected. The ocular palsies would also not be a feature. Similarly Sheehan's syndrome of pituitary necrosis might be expected to be associated with sudden onset of shock, perhaps with bloody spinal fluid and mental confusion, and not to evolve as slowly as did the signs of this patient. For the same reason the sudden onset of the effects of embolism would not be considered.

There is only one common cause of stupor and ataxia leading to mental confusion associated with nystagmus and bilateral external rectus paralysis, namely Wernicke's syndrome. Optic neuritis, occasionally with retinal hemorrhages, is commonly associated with it. The tendon reflexes are lost late in the course of the syndrome. Following the earlier studies of Alexander[1] and of Jollife and his associates,[4] there seems no reason to doubt that acute and severe thiamin deficiency is its particular determinant. The studies of Phillips and

co-workers[6] in this hospital appear to place the relationship to thiamin deficiency beyond any reasonable doubt. It is also well established that Wernicke's syndrome has a widespread effect on the nervous system, producing mental changes that are seldom completely reversible after the first two or three days, and that it is rapidly fatal if untreated. Indeed I know of no case that recovered before parenteral thiamin became available. It was then a postmortem curiosity. The prevalence of Wernicke's syndrome in chronic alcoholics has led to undue emphasis upon alcoholism as its cause. It has been forgotten that before the studies of thiamin treatment of chronic alcoholics, the most common single cause of Wernicke's syndrome was gastric obstruction. It was a common terminal episode in gastric carcinoma.[2] One of Wernicke's own cases had pyloric stenosis following the suicidal ingestion of sulfuric acid. Any form of recurrent vomiting may provide the background for its development, and hyperemesis gravidarum is a well known cause. A predominantly carbohydrate diet with thiamin deficiency led to its appearance in prisoners of war.[3] It has complicated the induction of hyperglycemia in an ill-nourished individual.[5]

In this patient the setting for the appearance of Wernicke's syndrome was complete, for not only had hyperemesis gravidarum existed for a considerable period but also final overloading of carbohydrate metabolism was induced by intravenous glucose. In the severe grades of deficiency reversal of symptoms by thiamin is not by any means immediate, and cardiac failure may still suddenly occur even during the first days of treatment.

I would conclude that the conditions present were: 1) Wernicke's syndrome; 2) bronchopneumonia; 3) hyperemesis gravidarum; 4) healed chronic recurrent hepatitis, nonalcoholic.

DR. FOLEY: Certain information relating to the terminal part of the patient's illness was withheld from Dr. Denny-Brown. After the neurologic consultant saw the patient he did three things in rapid succesion. His rapid test for urinary porphyrins was negative. He gave a test dose of neostigmine which had no effect. His first diagnosis was Wernicke's encephalopathy. Although the 100 mg. of thiamin he gave was not too little, it surely was too late.

The patient had been on streptomycin and penicillin for her infection, and no organism were recovered either pre- or postmortem.

The liver showed no evidence of the old hepatitis.

The heart was grossly normal but there was congestive heart failure, as evidenced by moderate pulmonary congestion and edema, small pleural effusions, slight ascites, and passive congestion of the liver and spleen. Microscopically the heart showed an acute interstitial myocarditis. Scattered in the interstitial tissue were small collections of large and small mononuclear cells and a few granulocytes and eosinophiles in slightly lesser numbers. In the septum were scattered foci of inflammatory cells, some degenerating fibers, but no actual necrosis. There was also some focal pulmonary atelectasis. Except for the nervous system the rest of the autopsy was within normal limits.

The brain was cut after fixation. No abnormalities appeared on the external surface or on multiple coronal sections. Special attention was paid to the mammillary bodies, the periaqueductal region, and the floor of the fourth ventricle, but no abnormalities were seen in the gross. After microscopic sections were examined we reviewed the gross material once again and could not convince ourselves of any change.

Sections were taken from peripheral nerves, spinal roots and ganglia, spinal cord, medulla, pons, midbrain, cerebellum, anterior and posterior hypothalamus, lenticular nucleus, thalamus, and several areas of cerebral cortex.

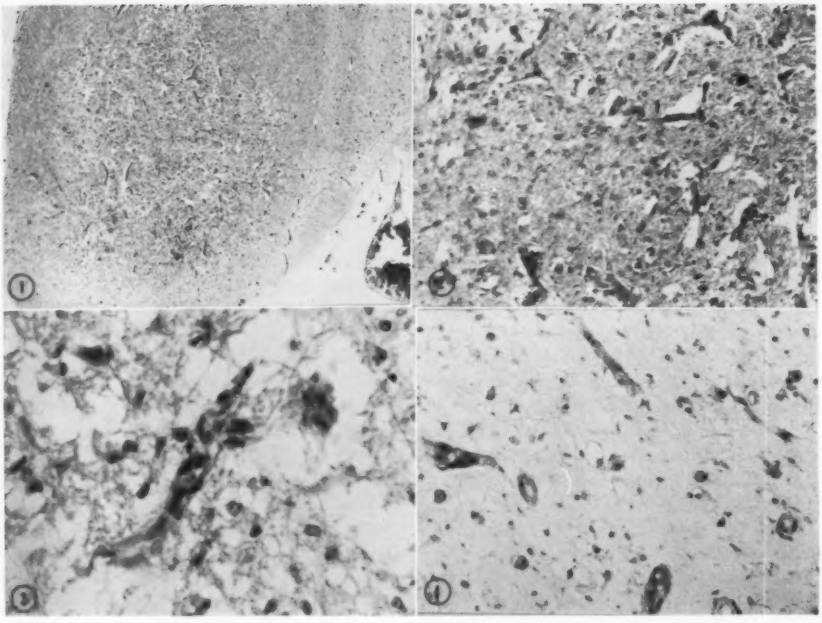


FIG. 1. Mammillary body. Hematoxylin and eosin.
FIG. 3. Mammillary body. Hematoxylin and eosin.
FIG. 2. Mammillary body. Hematoxylin and eosin.
FIG. 4. Dorsal motor nucleus of the vagus. Hematoxylin and eosin.

The most important changes were in the mammillary bodies and the dorsal motor nuclei of the vagus nerves. Satisfactory sections of all the oculomotor nuclei were not available. At low power (figure 1) the mammillary bodies showed a derangement of their architecture. There were large and small spaces in the tissue and the ground substance gave the appearance of being completely disrupted. The nerve cells were irregularly spaced and there was an excess of vessels with prominent cellular walls. On higher power (figure 2), nerve cells were not significantly reduced in numbers, but their appearance was very variable. All the nerve cells showed some distortion of their outline, as if they were pushed out of shape by the vacuoles in the ground matrix. Some nerve cells were destroyed, as manifested by dense pyknosis of the nucleus and an eosinophilic homogeneity of the cytoplasm. Many others, however, appeared viable, for although the cell membrane was irregular, it was intact, and the nucleus had retained its membrane, its usual chromatin appearance, and an intact nucleolus. The blood vessels seemed increased, not only in prominence but also in numbers. Most of the vessels showed proliferating cells in their walls (figure 3). Although this was largely an endothelial proliferation, in some of the larger vessels there seemed to be proliferation of the cellular elements of all coats. In one part of the section, a few poorly developed histiocytic macrophages were present about a vessel here and there. Despite these alterations of the ground substance, the nerve cells, and the blood vessels, there was very little in the way of either astroglial or micro-

glial change. No hemorrhages were present. The dorsal motor nucleus of the vagus showed a similar change, but to a lesser degree (figure 4). The vacuolization of the ground matrix was less intense, the nerve cells were affected in about the same degree, and the blood vessels showed a lesser degree of prominence and cellular proliferation.

These histologic findings are diagnostic of Wernicke's encephalopathy. The mechanism of the histologic change is obscure, except that, ultimately, it is one of the manifestations of thiamin deficiency. Opinions differ as to which of the elements of the histologic change is primary. In our experience, the amount of nerve cell destruction does not seem adequate to produce such an intense vascular response, and we are therefore doubtful that this is a primary affection of the nerve cells in these areas. It seems more likely that the primary change is in the blood vessels or in the poorly understood ground matrix of the structures involved.

The relation of the cardiac disease to the disorder of the brain is not altogether clear. The classical picture of beri-beri heart disease was not present in all its details. Although there was some congestive failure, the heart was not dilated or flabby, and an acute interstitial myocarditis is not enough to allow one to identify the etiology from the morphology. The cardiac changes in beri-beri, however, are still not clearly defined, either by the clinician or the pathologist, and for the time being we can only say that our knowledge of the spectrum of cardiac change in thiamin deficiency is regrettably incomplete. There is some reason to believe that, in a cardiac disorder of any cause, the tendency to congestive failure may be enhanced by a concomitant thiamin deficiency.

Certain features of Wernicke's encephalopathy need constant reemphasis. As Dr. Denny-Brown has pointed out, the association with alcoholism has made some clinicians think of it only in this regard. It may occur in any condition in which the circumstances are right for a nutritional defect, and especially it should come to mind as a cause of neurologic disorder in patients with pregnancy, with gastrointestinal malignancies, and other states that lead to cachexia. Another point to remember is that patients die of Wernicke's encephalopathy. The mere suspicion of the diagnosis justifies the immediate administration of thiamin. As you know, the eye signs may respond dramatically, but the mental changes, once established, are likely to be persistent for months or years.[7] The time for treatment, therefore, is before any mental changes have occurred. There can be no excuse for delay in therapy, especially when the therapeutic agent is so specific and the stakes are so high.

REFERENCES

1. Alexander, L.: Wernicke's disease: Identity of lesions produced experimentally by B_1 avitaminosis in pigeons with hemorrhagic polioencephalitis occurring in chronic alcoholism in man, Am. J. Path. 16:61, 1940.
2. Campbell, A. C. P., and Biggart, J. H.: Wernicke's encephalopathy (polioencephalitis hæmorrhagica superior): Its alcoholic and nonalcoholic incidence, J. Path. & Bact. 48:245, 1939.
3. Cruickshank, E. K.: Wernicke's encephalopathy, Quart. J. Med. 19:327, 1950.
4. Jolliffe, N., Wortis, H., and Fein, H. D.: The Wernicke syndrome, Arch. Neurol. & Psychiat. 46: 569, 1941.
5. Jones, F. A., and Robinson, V. C.: Wernicke's encephalopathy simulating diabetic coma, Lancet 2:907, 1947.
6. Phillips, G. B., Victor, M., Adams, R. D., and Davidson, C. S.: A study of the nutritional defect in Wernicke's syndrome, J. Clin. Investigation 31: 859, 1952.
7. Victor, M., and Adams, R. D.: The effect of alcohol on the nervous system, A. Res. Nerv. & Ment. Dis., Proc. 32:526, 1953.

CASE REPORT

Post-Seizure Purpura of the Head and Neck

Thomas C. Guthrie, M.D.

THE COMMONLY observed complications of a convulsion include local injury to the skin of the head and face. More extensive bleeding suggests intracranial injury and skull fracture. A patient is described who developed unusual widespread ecchymoses of the head and neck following a seizure.

CASE REPORT

A 22 year old white male college student suffered his first and only episode of loss of consciousness while playing cards. At the time he was irritated at the game and aware of an extremely tight shirt collar. According to a witness, he leaned forward, laughed vigorously, then fell backward to the floor, striking his occiput. His right arm twisted behind his back. During the two minutes of unconsciousness, the patient's face was red and suffused, his neck veins were distended and his eyes became discolored. The patient frothed at the mouth. Upon recovering consciousness, he was disoriented and confused for ten minutes, then slept soundly. The patient had no memory for these occurrences. He awoke without complaints, except for noticing his discolored eyes.

Past medical and personal history were negative. There was no history of a tendency to bleed.

Admission physical examination was negative, except for extensive subconjunctival hemorrhages bilaterally and marked eccymoses under both eyes. The skin of the entire head and neck and scalp showed a marked diffuse hemorrhagic rash which did not fade on diascopy. There was no purpura on the mucous membranes. The lower border of this discoloration ended exactly at the collar-line in the neck. The neurologic examination was negative.

Hospital workup included complete blood count, blood serology, urinalysis, bleeding and clotting time, prothrombin time, and fasting blood sugar. All were within normal limits. Roentgenographic examination of the chest and skull was normal. Examination of the spinal fluid was normal. An electroencephalogram showed an abnormal amount of scattered five to six per second high amplitude slow waves.

Special studies were carried out with carotid compression. Carotid compression on the right side caused no changes in electrocardiogram or electroencephalogram recorded simultaneously, but a decrease in heart rate from 108 to 60 per minute was noted. Similar compression of the left carotid artery produced no bradycardia and no changes in electrocardiogram or electroencephalogram.

While in the hospital, the patient had no convulsions. The purpura around his eyes and face cleared in two weeks, and he was discharged without medication. Follow-up examination one year later revealed that the patient had had no convulsions.

DISCUSSION

This young man had an abnormal electroencephalogram, which indicated his predis-

From the neurology service of the department of neuropsychiatry, Valley Forge Army Hospital, Phoenixville, Pennsylvania.

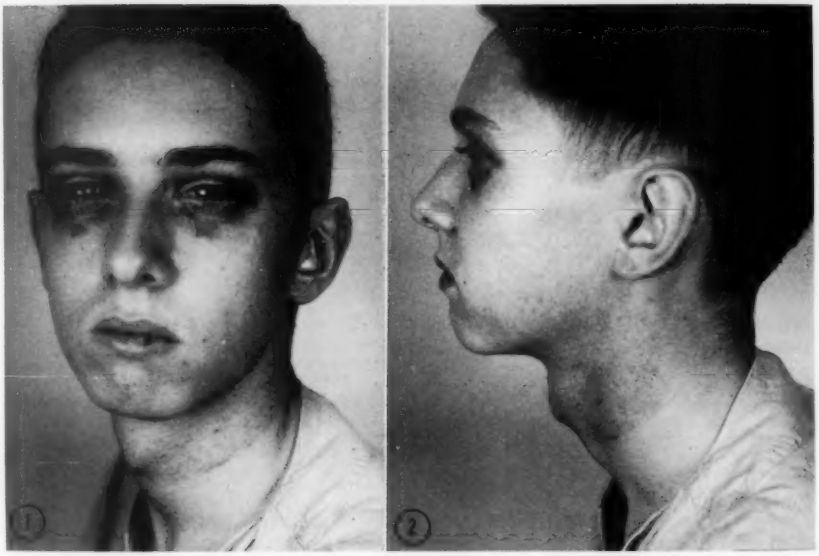


FIG. 1. Purpura of the head and neck following a seizure. FIG. 2. Lateral view showing lower border of purpura.

position to convulsions. His right carotid sinus when compressed caused a decrease of as much as 40 beats per minute in his cardiac rate. While wearing a tight shirt collar, the patient leaned forward and lost consciousness. Apparently the seizure was related to right carotid compression. The cerebral dysfunction may have been associated with cardiac slowing, lowered blood pressure, or reflex neural effects from the carotid compression. During the seizure, the patient's face was suffused with blood and his neck veins were distended. Following the vasodilatation of the superficial cranial vessels, the patient showed frank hemorrhages in the conjunctivae and around his eyes. The resulting purpura in the skin of his head and neck were sharply limited to areas above his overly tight collar.

Skin lacerations and local skin trauma are frequently seen in persons who have had a seizure. Extensive ecchymoses suggest skull fracture, especially basilar. In this case, the bleeding into the skin was an unusual complication of a seizure and was not related to skull fracture. Apparently the tight collar was a factor in the production of the skin bleeding, since it formed its lower boundary.

SUMMARY

The case history of a young man is presented who developed an unusual purpura of the face and neck following a generalized convulsion while wearing a tight shirt collar.

Author's present address:
12 East 68th Street, New York City

CASE REPORT

Ectopic Pinealoma

Ralph L. Drake, M.D., Bert E. Stofer, M.D. and Larry Vin Zant, M.D.

THE PRESENCE of a tumor of so-called pinealoma structure, occurring in areas of the brain other than the pineal body with the latter intact, has been described in only 12 reported instances. In these cases the various sites affected were the quadrigeminal plate, vermis of the cerebellum, the ventricular ependyma with diffuse infiltration, the infundibular region, anterior wall, and floor of the third ventricle, and pituitary body.

While the true nature of the so-called pinealoma remains unsettled, we are using as criteria for this type of growth the description by Russell:[1] "This comprises a tumor composed of solid masses of large spheroidal cells, separated by connective tissue stroma infiltrated in many areas by cells indistinguishable from lymphocytes."

Since the ectopic occurrence of this growth is rarely encountered, the report of a case with a different type of involvement seems justified.

REPORT OF CASE

A 22 year old white woman was admitted to the Wesley Hospital on March 9, 1953. For the previous three weeks she had complained of vertex head pain radiating to both occipital and frontal areas. One week later she noticed blurring of vision and diplopia on looking upwards and to the right with associated nausea and vomiting of three days' duration.

The general physical examination showed no abnormal findings. On neurologic examination the only abnormal finding was bilateral papilledema of one diopter. The cerebrospinal fluid examination showed a pressure of 450 mm. of water with 10 lymphocytes and 3 polynuclear leukocytes. The quantitative protein was 90 mg. per 100 cc. Electroencephalographic study was normal.

Radiographic study showed adequate filling of the lateral and third ventricles. There was a 1 centimeter shift of the ventricular system to the right with marked dilatation of the left inferior horn (figures 1 A and B).

At operation a firm, smooth tumor measuring 2x1x1 cm., pinkish-white in color and homogeneous on cut section, was removed from the left inferior horn of the lateral ventricle where it was attached to the inferior medial wall by a pedicle. The patient made an uneventful recovery from the operation and has not had any complaints for the past year.

Pathology: The specimen received in the laboratory was a pinkish-white mass 2x1x1 cm. It was ovoid in outline and tapered at one pole, suggesting the previous attachment by a short pedicle. The cut surface was homogeneous, glistening, and pink. No calcific areas were present.

Microscopic examination showed a circumscribed nonencapsulated tumor composed of two types of cells. The predominant cell was large, round to ovoid with moderately large nucleus. The nuclear membrane was sharp. The chromatin granules were variable in size and deep-staining. The cytoplasm was pink. Mitotic figures were absent (figure 2).

Scattered through the tumor were numerous small round hyperchromatic cells resembling lymphocytes (figure 3). Occasionally these cells were arranged in masses, frequently around the capillaries. No calcification or necrosis was found in any part of the tumor.

From the departments of neurology and pathology, Wesley Hospital, Wichita, Kansas.

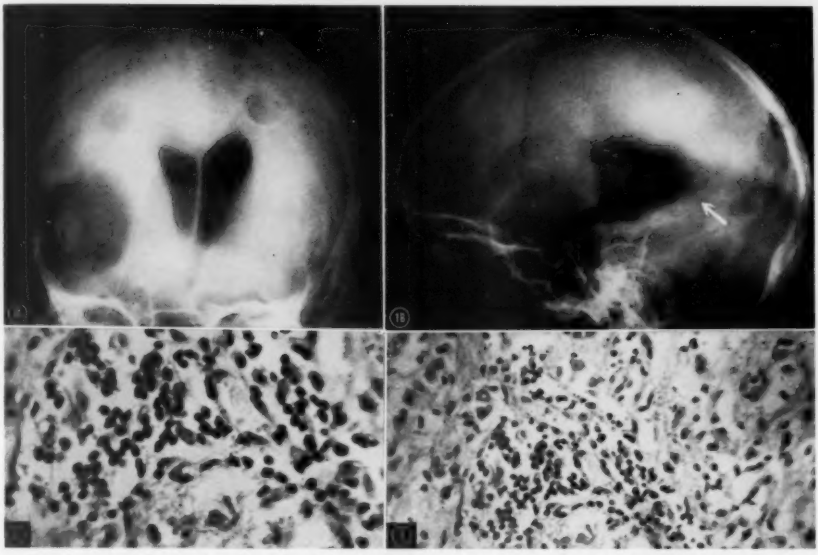


FIG. 1. *A* and *B*, showing the shift of the ventricular system and the dilatation of the left inferior horn. FIG. 2. High power photomicrograph showing mass of spherical cells, connective tissue stroma, and lymphocytic infiltration. FIG. 3. Low power photomicrograph showing cells resembling lymphocytes around a blood vessel.

DISCUSSION

There is considerable similarity between this tumor and reported cases of ectopic pineal tumor. The two cell types and arrangement of the cells are in keeping with this interpretation. Multiple seedings of the ventricle by metastatic pineal tumors have been reported. Steiner,[2] who reviewed the slides, suggested the possibility of other implants developing later.

It has been suggested by Russell that small ectopic tumors resembling the pineal gland are in reality teratomas. Multiple sections of our tumor have failed to produce any elements other than those found in the original slides.

SUMMARY

A circumscribed growth removed from the medial wall of the left inferior horn of the lateral ventricle with microscopic features of an ectopic pinealoma has been described.

The fact that the pineal body is considered to be normal in this patient rests upon the absence of clinical and roentgenographic evidence of pineal abnormality.

REFERENCES

1. RUSSELL, D. S.: The pinealoma: its relationship to teratoma, J. Path. & Bact. 56:145, 1944.
2. STEINER, GABRIEL: Personal communication.
3. BOCHNER, S. F., and SCARFF, J. E.: Teratoma of the pineal body, classification of the embryonal tumors of the pineal body; report of a case of teratoma of the pineal body presenting formed teeth, Arch. Surg. 36:303, 1938.
4. GLOBUS, J. H., and SILBERT, SAMUEL: Pinealomas, Tr. Am. Neurol. A. 1930, pp. 445-493.
5. HORRAX, G., and WYATT, J. P.: Ectopic pinealomas in the chiasmal region, J. Neurosurg. 4:309, 1947.
6. RUSSELL, W. O., and SACHS, ERNEST: Pinealoma: a clinicopathologic study of 7 cases with review of literature, Arch. Path. 35:869, 1943.
7. RAY, HOMER F.: Diffuse involvement of the brain by pinealoma, J. Philadelphia Gen. Hosp. 4:110, 1953.

CASE REPORT

Calcified Subdural Hematoma

J. Arthur MacLean, M.D. and Laurence F. Levy, M.B.

CALCIFIED subdural hematoma is an uncommon lesion. In 1952 Mosberg and Smith[1] reviewed the literature and found 20 cases. They added one of their own.

It is the purpose of this paper to report a further case and to draw attention to the fact that, should signs of increased intracranial pressure appear in a patient with a longstanding subdural hematoma who was previously asymptomatic, the presence of other pathology should be suspected.

Typical skull roentgenographic changes have been described in infants harboring a chronic subdural hematoma; similar changes may have occurred in this patient during adult life.

CASE REPORT

A 55 year old man was admitted to the hospital on October 12, 1952. He gave a poor and inconsistent history and most of the information was obtained from his relatives. He had always been an extremely capable worker, but during the last six months he had slowed down. He had become irritable, lacked concentration, and at times talked unintelligibly.

One week prior to admission he was involved in a minor motor accident with a truck. He stated that he did not see the vehicle until it was too late. Subsequently his behavior became strange, he talked vaguely, and he often stumbled and fell.

Twenty years prior to this admission he had been hospitalized with acute meningitis, from which he made an excellent recovery. In 1938 he had been employed on a tunnel construction job when he fell 30 feet and fractured some ribs. He was admitted to hospital but had no evidence of head injury. There was no other relevant history.

Physical examination

Intellectual level, concentration, understanding, and memory for recent events were seriously impaired. There was left homonomous hemianopsia. The fundi could not be visualized. Other findings were slight left astereognosis, position and vibration sense good, Romberg's sign positive to the right, slight right hemiparesis, and a broad based gait.

The electroencephalogram showed a random slow-wave focus in the right parietal region, extending into the right occipital and right posterior temporal regions, with mild generalized fast and slow dysrhythmia. The findings suggested a gross lesion, possibly neoplastic in nature and probably deep seated, and also some diffuse brain damage. In view of the electroencephalogram and visual field findings, the admission diagnosis was that of right parietotemporal neoplasm. This, however, did not account for the right-sided long tract signs.

Skull films showed an area of diffuse calcification in the left parietotemporal region measuring about 11 cm. in the anteroposterior direction and 6 cm. vertically. It lay in the shape

From the department of neurosurgery, New York University Post Graduate Medical School, New York City.

of a thin plate just beneath the bone of the calvarium. There was enlargement of the vault of the skull on the left, and the ethmoid and frontal sinuses on that side were enlarged. The left maxillary antrum appeared larger than the right, and the sphenoid sinus was unusually large. The pineal gland was not visualized. The radiologist suggested the diagnosis of calcified subdural hematoma.

Spinal puncture showed a pressure of 390 mm. of cerebrospinal fluid, a small quantity of which was removed. Protein was 120 mg. per cent. There were no white blood corpuscles.

October 16, 1952: Ventriculogram. A burr hole was made in the right posterior parietal region. The lateral ventricle was entered with difficulty. Only 5 cc. of fluid was obtained and a like quantity of air injected. A trephine opening was placed in the parietal region of the left side. The dura was seen to be extremely hard. It was incised with some difficulty and a large quantity of xanthochromic fluid escaped. The inner membrane was noted to be as thick as the outer. No attempt was made to enter the lateral ventricle. A rubber drain was inserted and removed after 24 hours. Roentgenograms showed a small quantity of air in each lateral ventricle. The entire ventricular system was shifted to the left. There was insufficient filling for further evaluation.

The problem remained as to whether the shift in the ventricular system was due to contraction and atrophy on the left side secondary to the subdural hematoma, or whether there was also an expanding lesion on the right side.

October 17, 1952: Electroencephalography was repeated the day following the ventriculogram and showed a tracing so different from the previous one that it was impossible to make any comment upon the nature or location of the intracranial lesion. In view of these findings it was decided to perform further air studies before proceeding to craniotomy.

October 18, 1952: Pneumoencephalography. The entire ventricular system was seen to be markedly shifted to the left of the midline. Both lateral ventricles were enlarged, the left more so than the right. Incomplete filling of the right lateral ventricle did not allow an expanding lesion on that side to be completely excluded. The picture, however, was thought to be more suggestive of retraction due to atrophy of the left cerebral hemisphere and shrinkage of the hematoma than it was of an expanding lesion on the right side (figure 1). (Davidoff and Dyke[2] reported paradoxical shift of the ventricles toward the side of the lesion in similar cases in children.)

October 22, 1952: Left temporoparietal craniotomy. Using the craniotome, a circular temporoparietal bone flap was swung on the temporalis muscle. Its center was located above the middle of the calcified area and it was about 3 inches in diameter.

Immediately after the bone flap was reflected, the very hard subdural mass was observed. The dura mater was incised and reflected easily from the outer calcified layer of the hematoma, which was so firm as to be solid when tapped with an instrument. This latter was removed piecemeal and disclosed the cavity of the hematoma which had been opened nine days before. The inner membrane of the hematoma was likewise calcified and solid and was removed (figure 2). The arachnoid was quite free from the inner membrane and was only slightly glassy in appearance. There was little bleeding. The dura mater was loosely sutured in position and the bone flap replaced. A burr hole was made in the right temporal region. The dura and brain beneath were normal.

The patient's postoperative condition was stormy for several days, but he gradually improved.

November 10, 1952: Pneumoencephalography showed that there had been some shift of the ventricular system back toward the midline but otherwise no change in pattern. The dilatation of the left lateral ventricle was seen to be greater than previously thought. The right lateral ventricle was again poorly filled. The aqueduct and fourth ventricle were not visualized. A few remaining areas of calcification were noted.

November 16, 1952: Cerebrospinal fluid pressure 300 mm.; protein 70 mg. per cent; white cell count 8 per cu. mm. General condition—improving satisfactorily. The patient had been out of bed and was walking on his own.

November 19, 1952: Electroencephalogram. Abnormal record showing, besides some generalized dysrhythmia, a slow-wave focus in the right hemisphere posteriorly and another in the left frontomotor-temporal regions. This tracing much resembled the last.

On examination the patient's orientation, memory, and concentration were good. The left homonomous hemianopsia was unimproved. The hemiparesis had disappeared. Sensation to pinprick was normal but position sense poor. The patient no longer stumbled or walked on a broad base. He was discharged for observation on November 20, 1952, with the diagnosis of calcified subdural hematoma.

He was readmitted on December 19, 1952. For the first week after discharge he had been much improved. He was alert and conducted himself about the house in an excellent manner.

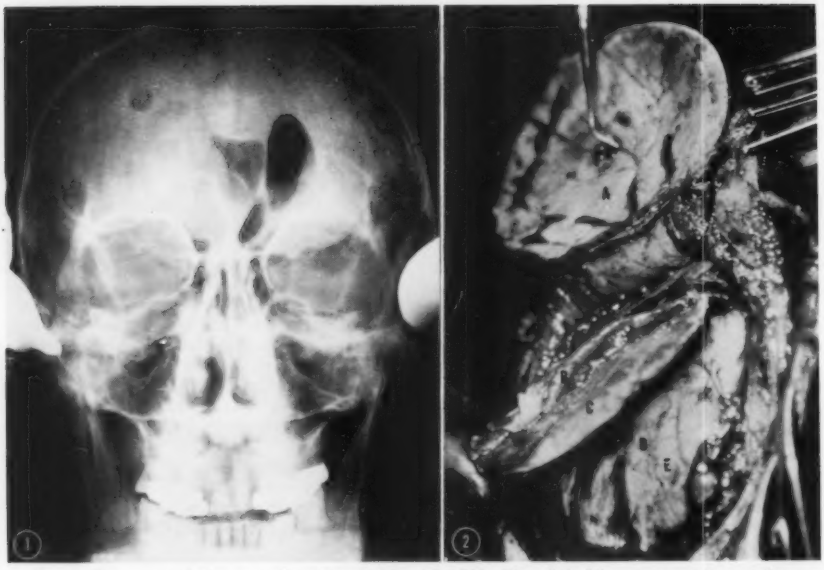


FIG. 1. Pneumoencephalogram performed on October 18, 1952. The calcified hematoma can be seen beneath the parietal bone on the left side. The ventricular shift towards the side of the hematoma should be noted.

FIG. 2. Operation October 22, 1952. The bone flap (a) has been turned back to reveal the dura (b), partly reflected from the outer calcified layer of the hematoma (c). The brain is just visible through that portion of the inner layer (d), which has been removed to expose the underlying arachnoid (e).

About ten days after his return home he began to get unsteady on his feet, and became increasingly forgetful and abstracted, as he had been prior to surgery. A lumbar puncture had shown his pressure to be elevated. Degeneration was progressive from then on. In the few days prior to admission he vomited several time and was extremely vague.

Examination showed his skull flap to be elevated and tense. The fundi showed congested veins but no papilledema. Visual fields could not be tested. There was a right hemiparesis, but the upper limb reflexes were more active on the left side.

Electroencephalography showed focal slow abnormality in the right hemisphere posteriorly and to a lesser extent in the left motor-parietal region, as well as a generalized, slow dysrhythmia.

His condition continued to deteriorate. He developed a chest infection which delayed treatment, and despite all efforts, which included further air studies and reexploration of the operative site, he became increasingly comatose and died on January 2, 1953.

Autopsy report

There was no remarkable pathology outside the skull. When the skull was opened, the dura mater of the left side was seen to be thickened and calcified in some portions. That of the right side was normal for a man of his age. Externally, the convolutions of the brain were slightly flattened. On the inferior surface of the right occipital lobe a hemorrhagic area was seen, and internally a firm mass was palpable. On sectioning the brain this mass was seen to be a tumor involving the entire right occipital lobe. It did not involve thalamus, basal ganglia, nor internal capsule. It deformed but did not occlude the lateral ventricle in its posterior horn. Microscopic section showed this tumor to be a glioblastoma multiforme.

DISCUSSION

Although this case represents a frank diagnostic error in that an attempt was made to interpret all symptoms in terms of

the calcified subdural hematoma, it is reported because it contains certain points of interest:

1. Calcification within a subdural hematoma is a rare lesion. Mosberg and Smith[1] reported a case and found 20 further cases in the literature. In addition to their cases, there are these further reports: Wertheimer and Dechaumes,[3] Schwartz and Collins,[4] Marinacci, Rand, and Marinacci,[5] and Newell,[6] who made a passing reference to having seen two cases but did not describe them.

2. In retrospect it seems difficult to understand why the correct diagnosis was not apparent. However, the notoriously false localizing signs associated with subdural hematoma, the rarity of two lesions at the same time, and the knowledge that in chronic lesions of this nature, the retraction of the hematoma may cause a paradoxic shift of the ventricular system toward the site of the lesion, were the factors responsible for the error. Mosberg and Smith[1] emphasized that patients with this condition may be quite asymptomatic, and it seems that when a patient with a longstanding chronic subdural hematoma, which was previously silent, develops the signs of an intracranial lesion, the possibility of this being due to other causes must be entertained.

3. Davidoff and Dyke[2] pointed out that children with chronic subdural hematoma develop secondary changes in the skull which can be seen on plain x-ray films. They consider that the increased intracranial pressure early in the disease causes an enlargement of the skull and middle fossa. As the hematoma shrinks, the skull responds to the lessened intracranial pressure by a thickening of the bone overlying the hematoma and hypertrophy of the frontal and ethmoidal sinuses.

Boyd and Merrell[7] reported a case of a 55 year old man in whom there were excellent grounds for believing that a hematoma developed during adult life some 26 years

This patient showed changes previously. similar to those reported by Davidoff and Dyke. They remarked that if the same factors responsible for the changes in the infant skull are present in their case, it is surprising that the adult possesses such a lability of structure and capacity for compensation.

Mosberg and Smith's case showed many similar features, but the duration of the hematoma is unknown.

The case reported here showed some similarity. There was enlargement of the vault, widening of the middle cranial fossa, enlargement of the ethmoid sinuses, and increase in the number of mastoid air cells on the side of the lesion. The left frontal sinus was larger than its fellow.

These findings are not grossly abnormal and, without a skull roentgenogram taken 20 years ago, it is not possible to assert that the patient did not have them since childhood. However, there is strong presumptive evidence to suggest that the patient had developed his hematoma between 15 and 20 years before and that subsequently his skull changed in shape.

The majority of cases in which the hematoma originated in childhood have a history of mental deficiency and seizures. The patient was very alert up to six months before his operation, with no history of seizures or neurologic disease. Twenty years before he suffered from acute meningitis, and 15 years before was hospitalized after a fall of 30 feet. His son remembered that during the last ten years his father had complained of having difficulty in getting hats to fit. Presumably during that time his head had been changing in shape.

It is suggested that in this case the skull changes occurred during adult life.

SUMMARY

1. A case of calcified subdural hematoma is reported. There are 24 other documented cases of calcified subdural hematoma in the literature.

2. In this case the subdural hematoma had remained quiescent for many years, and only came to light when the patient came

under investigation for intracranial symptoms due to the development of a brain tumor. The localizing signs associated with subdural hematoma are notoriously false, and an attempt was made to explain the entire picture in terms of the one lesion—the subdural hematoma.

The necessity for suspecting other pathology when a patient with a previously quiescent, longstanding subdural hematoma develops increased intracranial pressure is stressed.

3. Roentgenographic findings similar to those noted by Davidoff and Dyke as occurring in children with chronic subdural hematoma, and by Boyd and Merrell as occurring in adults, were observed in this case. The surprising plasticity of the adult skull is remarked. It had previously been thought that changes of this type could only occur in childhood.

REFERENCES

1. Mosberg, W. H., and Smith, J. R.: Calcified subdural hematoma, J. Nerv. & Ment. Dis. 115:163, 1952.
2. Davidoff, L., and Dyke, C.: Relapsing juvenile chronic subdural hematoma, Bull. New York Neurol. Inst. 7:95, 1938; Chronic subdural hematoma, Bull. New York Neurol. Inst. 7:112, 1938.
3. Wertheimer, P., and Dechaume, J.: Les hematomes sous-duraux calcifies, Acta psychiat. et neurol. 24:731, 1949.
4. Schwartz, C. Wadsworth, and Collins, L. C.: The Skull and Brain Roentgenologically Considered, Springfield, Illinois: Charles C Thomas, Publisher, p. 110, 1949.
5. Marinacci, A. A., Rand, C. W., and Marinacci, H. K.: EEG findings in chronic subdural hematoma of infancy and early childhood, Bull. Los Angeles Neurol. Soc. 16:253, 1951.
6. Newell, R. R.: Calcification in brain tumors, Surg. Clin. North America 3:775, 1923.
7. Boyd, D. A., and Merrell, J. P.: Calcified subdural hematoma, J. Nerv. & Ment. Dis. 98:609, 1943.

■ The first fact I have to speak of is, that a transversal section of the posterior columns, instead of being followed by the loss, or even a diminution, of sensibility, seems to produce an increase in the amount of this property; in other words, I have found that the section of these pretended only channels of the sensitive impressions, instead of preventing them from passing, allows them, on the contrary, to pass more freely, so that instead of anæsthesia there is hyperæsthesia. In certain animals, and especially in rabbits and sheep, it is very easy to ascertain that there is a very great increase in sensibility in the various parts behind the section. Before the operation, in rabbits, the most energetic pinching of the skin produces agitation, but no shrieking; after the operation, on the contrary, the least pinching produces shrieking, and a much greater agitation. Sometimes the hyperæsthesia is so considerable that the least pressure upon the skin makes the animal shriek. Whether the operation is performd in the lumbar, the dorsal, or the cervical region, the phenomena are always the same; that is, there is a manifest hyperæsthesia in the various parts of the body which receive their nerves from the part of the spinal cord which is behind the section. It has been so in all the animals I have operated upon, and I have already made this experiment upon animals belonging to more than twenty species.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Neurology

BOOK REVIEWS

Hyperostosis Cranii

Sherwood Moore, M.D. 1955. Springfield, Illinois: Charles C Thomas, Publisher. 226 pages. $10.50.

THE present monograph, written by a radiologist of wide experience whose interest in the subject extends over many years, deals with what may be called "idiopathic" cranial hyperostosis. Although the work is designed as a review of the whole field ranging from electroencephalography to paleopathology, its main substance is based upon the painstaking roentgenographic analysis of the skulls of over 10,000 patients and 1,500 anatomic specimens. From this material the author establishes an incidence of 12.4 per cent in adult female skulls and 1.08 per cent in the male, thus verifying the well recognized preponderance of the condition in women. Four major types are identified, namely, the familiar hyperostosis frontalis interna, a rare frontoparietal form, a more restricted variety of density of the frontal squama termed nebula frontalis, and hyperostosis calvariae diffusa. It is recognized that these subtypes are somewhat arbitrary, that they may appear in varying combinations, and that one form may become transformed into another over a period of time. From this it is concluded that they are merely different stages of the same process. As to the nature of the underlying process, the author makes a good case for his view that the hyperostosis has its origin in an expansion of the diploe rather than in primary new formation of compact bone from the dura, as is generally thought.

So far this is perfectly acceptable natural history. But when the author attempts, as others have done before him, to establish the broader thesis that cranial hyperostosis is a part of a recognizable clinical syndrome, he becomes anything but convincing. The supposed syndrome, derived in this case from an analysis of the hospital records of 522 patients with hyperostosis and a comparison with the records of 1,227 male and female patients without it, is composed of a heterogeneous group of symptoms which might be expected in any group of women seeking medical care in a large clinic. Chief among them are headache, obesity, and a variety of psychoneurotic symptoms, but included also are convulsions beginning late in life, insanity, abnormality of thyroid function, and muscular weakness and fatigue. It should be said that no statistical validation of the correlation of any symptoms with hyperostosis is given. It is also of interest that the author found an incidence of incipient hyperostosis in the skulls of a group of 269 healthy young women, candidates for admission to a school of nursing. Moreover, the incidence was essentially the same among those who were

accepted, those rejected, and those later dropped from school for incompetence. Indeed the author's own data tend to confirm one in the view of that careful student of the subject, Henschen, to the effect that frontal hyperostosis is no more than a commonplace postmenopausal characteristic.

The writer's style is often obscure and difficult to follow and there are more than an allowable number of typographic errors. None of the numerous graphs is numbered for cross reference to the text, adding further to the difficulty in reading. All in all the book has little to offer to the clinical neurologist in either a practical or theoretical way.

R. B. R.

Correlative Neurosurgery

Edgar A. Kahn, Robert C. Bassett, Richard C. Schneider and Elizabeth Caroline Crosby. 1955. Springfield, Illinois: Charles C Thomas, Publisher. 413 pages. $19.50.

This is a volume on clinical neurosurgery oriented towards neuroanatomy. Written by the pupils of Max Minor Peet, to whom the book is dedicated, it presents clearly the viewpoint of the University of Michigan division of neurological surgery towards all phases of not only clinical neurosurgery but the diagnostic specialties relating to it. Thus chapters are written on the roentgenologic examination of the skull, the electroencephalographic localization of intracranial tumors, the use of radioactive isotopes in the diagnosis and localization of brain tumors, endocrinology and metabolism in neurosurgical practice, and plastic closure of scalp defects, as well as all major subjects of neurosurgical interest.

In the preface, Dr. Kahn states that the book has been written primarily for young neurosurgeons who are about to commence practice. In the 23 chapters of the book the major interests of the neurosurgeon are presented by different authors, each of whom has his own background. As the author states, this has meant that in some cases a compromise has had to be made in the selection of material and also in the style of the book. The varied literary efforts of the authors, however, do not detract from the fundamental excellence of the monograph. It is difficult to choose outstanding contribution, but certainly the chapters on electroencephalography, on tumors of the sellar and third ventricular regions, on pain, and on craniocerebral trauma are particularly well presented.

The large, excellent illustrations appearing on almost every page of the book are a great help in understanding the text and greatly simplify the correlation which the authors attempt to make between anatomy, physiology, and clinical symptomatology. The index is quite extensive. Following each chapter a select but quite adequate bibliography is appended. This book deserves a wide reading audience, not only among neurosurgeons but also neurologists, neuroanatomists, and neurophysiologists. It presents some of the important aspects of clinical neurosurgery to which the more basic disciplines can contribute significantly.

A. E. W.

NEWSLETTER

JULY, 1955

Walter O. Klingman, President
Francis M. Forster, President-Elect
Augustus S. Rose, Vice-President
Thomas W. Farmer, Secretary
Joseph L. Whelan, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

Can Neurologists Be Taught to Teach?

Can neurologists, intending to pursue a full-time academic career in teaching and research, profit from an eight-month "finishing" course in the art and technic of teaching and research? Dr. Julius Comroe, creative authority on medical education and professor of physiology and pharmacology at the Graduate School of Medicine of the University of Pennsylvania, believes they can! And to prove his thesis, Dr. Comroe is developing such a program, for which he is recruiting a faculty of scientific educators with proved teaching ability from the Graduate School of Medicine, as well as many noted teachers, editors, clinicians, and scientists outside of the Philadelphia area.... Supported by a grant from the National Institute of Neurological Diseases and Blindness, the first session of the new program, the only one of its kind in the U.S.A., will begin in late September 1955 and end in May 1956. Prospective candidates must have either Board certification or fulfill most of requirements therefor. Preference will be given to applicants who have been selected by their own medical school faculty for advanced training, with the understanding that they return to their own schools for full-time careers in teaching and research.... The program has three specific aims: modified do-it-yourself training in the skills of medical teaching, writing, and administration; training in advanced and specialized scientific technics to round out the trainee's background for advanced medical research; and elective training and supervised research leading to the degree of doctor of science (Med.).... Instruction in the teaching art will follow a practical group technic, in which each group member will serve in turn as lecturer or seminar chairman and then as a part of a critical audience. Each lecture or seminar will be recorded so that the speaker can benefit from playbacks and audience reaction. Recordings will be kept and compared with later performances in order to gauge progress. Finally, the trainees will be assigned acting teaching responsibilities under supervision. In these and other teacher-training activities, no attempt will be made to attain uniformity in teaching, but rather to develop those teaching technics best suited to the personal attributes of each physician. Special seminars on medical writ-

ing, library utilization, and the broad application of the basic medical sciences to clinical problems will also be given.... The part of the program devoted to training in advanced and specialized scientific technics will include courses in statistics and mathematics for medical research; the design of experiments; recent advances in electronics, biochemistry, and biophysics; consideration of modern research technics and methods; seminars on critical evaluation of medical literature and the philosophy of research.... Finally, the training and supervised research in clinical neurology and the neurologic sciences will be offered as elective courses acceptable as credit toward the degree of doctor of science (Med.).... Since many of the trainees eventually may become departmental chairmen, special seminars will be offered on medical administration (including budgeting, personnel selection, hospital administration, and voluntary health plans).... All inquiries should be addressed to Dr. Julius H. Comroe, Jr., Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

Von Sallmann Joins NINDB Bethesda Staff Dr. Ludwig von Sallmann, nationally noted investigator and professor of ophthalmology at Columbia University College of Physicians and Surgeons, has been appointed a visiting scientist to direct and expand the intramural program in eye research at the National Institute of Neurological Diseases and Blindness starting August 1st. Dr. von Sallmann, recipient of the Proctor Award in 1951, is particularly noted for his work in ocular physiology and pharmacology, especially as related to cataract and glaucoma.

Senate Raises NINDB Almost $3 Million On June 6, the Senate voted to raise the budget of the National Institute of Neurological Diseases and Blindness $2,989,000 over the allowance made by the House of Representatives, which represents an increase of $3,739,000 over the Executive budget for the fiscal year 1956. This action could give NINDB a total budget of $11,850,000. These figures, however, are not necessarily the final appropriation figures for the fiscal year 1956, which will be determined in conference between the Senate and the House.

* * * * * *

Baker Speaks on Neurological Disorders in Industry As chairman of the National Committee for Research in Neurological Disorders, A. B. Baker addressed a large and mixed audience at a special luncheon at the La Salle Hotel in Chicago (May 24). The subject of his talk was the "Role of Research in the Restoration of the Neurologically

Disabled to Productivity." An associate speaker was the Hon. Maxwell M. Rabb, secretary to President Eisenhower's Cabinet, who spoke on the "Social and Economic Importance of Providing Job Opportunities for the Rehabilitated Worker." In addition, the luncheon meeting was preceded and followed by the nation's first conference on neurologic disorders in industry, which was sponsored by the Chicago Association of Commerce and Industry, the Illinois Epilepsy League, the Council on Industrial Health of the American Medical Association, and the National Epilepsy League. Awards for outstanding contributions were presented to William G. Lennox, Harvard Medical School, and Nicholas P. Dallis, creator of "Rex Morgan, M.D."

Harvey Tompkins Feted in Washington

A spirited gathering of associates and friends convened in Washington's famous National Press Club (May 31) to honor the contributions of Harvey J. Tompkins to the VA medical program. Dr. Tompkins is leaving his post as chief of the VA psychiatry and neurology service to assume directorship of the new Riis Mental Health Pavilion of St. Vincent's Hospital in New York City. Passing from cocktails to dinner, a lively program of anecdotes, poems, and eulogies extolling Dr. Tompkins were presented under the deft direction of Robert E. Adkins, executive officer of the VA department of medicine and surgery. Present at the party were members of the psychiatry and neurology central office and field staffs; former VA Chief Medical Director Paul B. Magnuson, and the present Chief Medical Director, William S. Middleton, and distinguished guests....Successor to Dr. Tompkins is Jesse F. Casey, formerly chief of the psychiatry division, VA Central Office.

Voice Recordings of AAN Members to be Preserved

At the AAN meeting in Houston (April 25-30), A. Theodore Steegmann, chairman of the history committee, began a unique project whereby voice recordings of prominent AAN members will be made for the permanent archives of the Academy. Howard Fabing's presidential address in Houston was thus recorded, and informal interviews were held with many AAN officers and ex-officers. Recordings were made of their verbal accounts of the highlights in their careers, which now can be handed down to posterity.

AAN Registry of Positions in Neurology

Under the chairmanship of Dr. Maynard M. Cohen, assistant professor of neurology at the University of Minnesota, the Academy is developing a registry of available positions in neurologic teaching, research, and practice. Qualified individuals interested in such positions in neurology should write to

Dr. Cohen. Similarly, universities and other institutions, or physicians in private practice seeking individuals trained in clinical neurology or the neurologic sciences, should also make their needs known to the registry. Correspondence on all inquiries will be kept confidential. All communications regarding the registry should be sent to Dr. Cohen at the University of Minnesota, Minneapolis 14.

O'Leary to Head Scientific Program at 1956 AAN Meeting James L. O'Leary, professor of neurology at Washington University, will head the scientific program for the annual AAN meeting at the Hotel Jefferson, St. Louis (April 23-28, inclusive). A preliminary meeting of the program and special courses committees will be held in St. Louis in January 1956. The general program chairman for the 1956 meeting is Dr. F. L. Stone, assistant to the vice chancellor, University of Pittsburgh.

Briefs The Liberty Mutual Insurance Company of Boston, the Haynes Memorial Department of the Massachusetts Memorial Hospitals, in cooperation with the Boston University School of Medicine, have established an industrial rehabilitation department and neurosurgical service for the treatment of paraplegic patients, the first such project to be undertaken by a private company.... Robert Jaffe, Howard P. Krieger, Milton Sapirstein, and Hans Strauss, all of the Mount Sinai Hospital, have been elected to membership in the New York Neurological Society.... Prof. O. L. Zangwill of Cambridge University, England, lectured on "Amorphosynthesis and Spatial Agnosia" at the Mount Sinai Hospital, May 5th.... A recent lecturer at the National Institute of Neurological Diseases and Blindness was J. Purdon Martin, Senior Physician, National Hospital, Queen Square, London, who spoke on the "Cerebral Mechanisms for Emotional Movements."... Other recent and distinguished visitors from London to the U.S.A. were Dr. Denis Williams, Sir Henry Hallett Dale, and Lord Edgar Douglas Adrian, the latter two being Nobel Prize laureates in physiology and medicine.

Percival Bailey

a Brighter Prognosis for your

HERPES ZOSTER PATIENTS

when you use

PROTAMIDE®

(Sherman)

because published studies* show:

"Good to excellent results" in more than 80%, with "almost immediate improvement."

Prompt recovery in more than 90% when Protamide is started in the first week of symptoms.

Why not use Protamide first?

. . . for herpes zoster, post-infection neuritis, chickenpox, and other nerve root pain such as tabes dorsalis.

A sterile colloidal solution prepared from animal gastric mucosa . . . denatured to eliminate protein reaction . . . completely safe and virtually painless by intramuscular injection.

CLINICAL DATA ON REQUEST

*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

SHERMAN LABORATORIES

BIOLOGICALS • PHARMACEUTICALS

WINDSOR • DETROIT 18, MICHIGAN • LOS ANGELES

BALDPATE, Inc.

Geo. 2131 Georgetown, Mass.

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of
psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment;
electric shock treatments, sub-coma and deep coma insulin therapy when indicated.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. Schlomer, Medical Director

Reg. U.S. Pat. Off.

MEASURE Sensory Changes

The Bio-Thesiometer® enables you to make improved sensory tests because it **MEASURES** sensory changes. The results are expressed in numbers as they are in measuring blood pressure, temperature or other quantitative tests.

In addition to giving you quantitative and diagnostic data in your first test, owners emphasize "it is also valuable in following the progress of the disease, whether there is improvement or lack of improvement."

The Bio-Thesiometer® test replaces qualitative and non-standardized tests of sensation. The results are expressed in relative or absolute units which have exactly the same meaning to all those making such tests.

The Bio-Thesiometer® is a new tool for the diagnosis of many conditions in which the nervous system or vascular system is involved. May we send you complete information? Write to

BIO-MEDICAL INSTRUMENT COMPANY
20 Munn Road Newbury, Ohio

FOUNDED 1879

RING SANATORIUM

Eight miles from Boston

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff. *Courtesy privileges to qualified physicians.*

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts Telephone MIssion 8-0081

Products and Services...

PAMINE (BROMIDE) AND PHENOBARBITAL, ELIXIR

and Phenobarbital in the same proportion as

A pleasant-tasting elixir containing Pamine and Phenobarbital in the same proportions as in the tablets has been recently introduced by The Upjohn Company, Kalamazoo, Michigan. Each 5 cc. (approximately one teaspoonful) contains: Phenobarbital 8 mg. (⅛ gr.); Methscopolamine Bromide 1.25 mg.; Alcohol 20 per cent.

Action and Uses: Pamine, a new parasympatholytic agent, inhibits gastric secretion, producing both a decrease in total volume and in acidity. It also decreases gastrointestinal motility. Phenobarbital is added because of its sedative action, which is desirable for the highly excitable, tense and apprehensive patient.

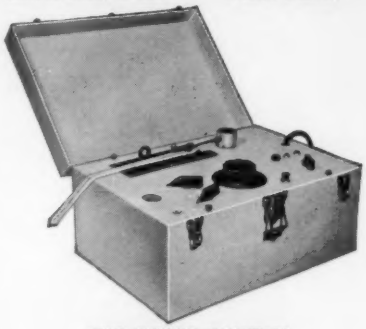
For use as an adjunct in the management of peptic ulcer and gastric disorders associated with hyperacidity and hypermotility. It may also prove useful in the symptomatic relief of "functional" nausea and vomiting, ureteral and vesical spasms, acute nonspecific diarrheas associated with hypermotility of the gastrointestinal tract, and dairrhea associated with certain antibiotics.

Administration and Dosage: The average dosage is 1 to 2 teaspoonfuls three or four times daily, depending upon the requirements of the patient and tolerance to the side effects of the drug.

GARCEAU ELECTROENCEPHALOGRAPHS

A. C. Operated
Inkless Writing
Shipped Ready to Run

No Batteries
Requires no Shielding
Prompt Delivery



THE JUNIOR GARCEAU ELECTROENCEPHALOGRAPH

A simplified inexpensive instrument for recording electrical potentials of the brain. Built-in interference eliminators permit use anywhere. Inkless records — no photography or film development required. Instantaneous localization with any 2 of the 10 leads.

Price $575.00 Complete.

All Garceau Electroencephalographs operate entirely from the 115 volts 50 or 60 cycle power lines.

Write for Literature

ELECTRO - MEDICAL LABORATORY, INC.

South Woodstock 15, Vermont

Pioneer makers of the electroencephalograph

HALL-BROOKE

An Active Treatment Hospital

A licensed private hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

A high ratio of staff to patients.

Large occupational therapy building with a trained staff offers complete facilities for crafts, arts and recreation. Full program of outdoor activities.

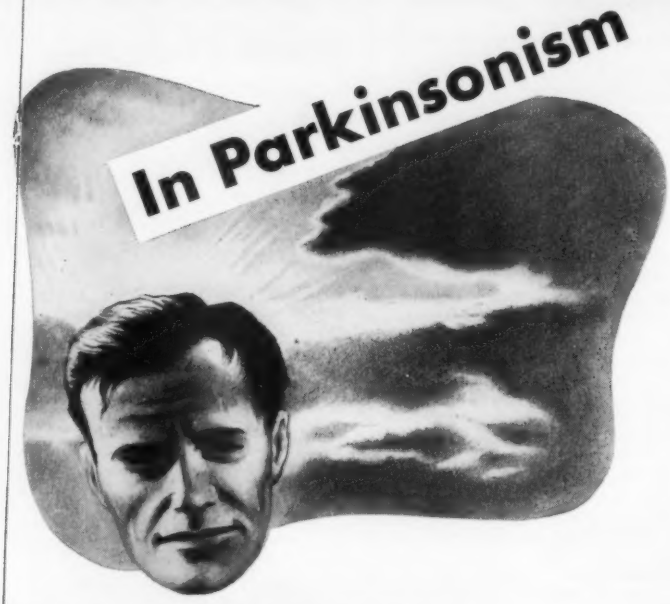
Each patient is under constant, daily psychiatric and medical supervision.

Located one hour from New York on 120 acres of Connecticut countryside.

HALL-BROOKE

Greens Farms, Box 31, Conn., Tel.: Westport, CApital 7-5105

George S. Hughes, M.D.
Leo H. Berman, M.D.
Alfred Berl, M.D.
Louis J. Micheels, M.D.
Robert Isenman, M.D.
Blanche Glass, M.A.
Mrs. Heide F. Bernard and
Samuel Bernard, Administrators



Detoxicated Scopolamine

One-sixth as toxic as Scopolamine[1]
Does not induce tolerance[2]
Acts in about half the time required by Scopolamine[3]
Can be used to supplement the effect of other drugs

Trial supply and information on request

GENO SCOPOLAMINE

1. Am. J. Pharm. — 117:319-326, 1945 2. N. Y. State Journal of Medicine 49/1285
3. Conference National Academy of Sciences Sept. 9, 1950

LOBICA-DEBRUILLE, INC. • 1841 Broadway, New York 23, New York

---

FOR ANTI-FLATULENT EFFECTS IN INTESTINAL DYSFUNCTION

EUCARBON®

Composition: Each tablet contains carbon by phenath. grade, precipitated sulfur, peppermint oil and fennel oil in an activated charcoal base. Action and Uses: Mild laxative, adsorbent, carminative and a purifier. For use in indigestion, hyperacidity, bloating and flatulence. An excellent detoxifying substance with a wide range of uses in dermatology. Administration: 1 or 2 tablets daily ½ hr. after meals. SUPPLY: Tins of 100.

SEDATIVE AND EUPHORIA FOR NERVOUS, IRRITABLE PATIENTS

VALERIANETS-DISPERT®

TASTELESS, ODORLESS, NON-DEPRESSANT SEDATIVE & EUPHORIC

Each Chocolate Coated Tablet Contains Ext. Valerian (highly concentrated) 0.05 Gm. dispergentized finely subdivided for maximum efficiency.

Indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, cardiac and gastrointestinal neuroses, menopausal and menstrual molimena, insomnia.

Dose: 1 or 2 tablets t.i.d. supply Bottles of 30, 100, 300 tablets.

A MODERNIZED METHOD FOR PREPARING BUROW'S SOLUTION U.S.P.

PRESTO-BORO®

In Tablets or Powder in envelopes (ALUMINUM SULFATE and CALCIUM ACETATE)

FOR USE AS AN ASTRINGENT and TOPICAL DRESSING

(U.S. Pat.)

Dissolve in plain water as directed for preparing astringent Burow's Solution for treatment of Swellings, Inflammations, Sprains. Antipruritic, decongestive action. Accurate uniform dosage. Stable, Lead free.

FOR PULMONARY CONDITIONS

TRANSPULMIN®

3% solution Quinine with 2½% Camphor for Intramuscular Injection

AVAILABLE AT ALL PHARMACIES

STANDARD PHARMACEUTICAL CO., INC., 253 W. 26th ST., NEW YORK

ADJUNCTIVE CHEMO-PSYCHOTHERAPY . . . *in tablet form*

Creates sense of well-being, increasing rapport and receptiveness to psychotherapy

Crystalline Alkaloid Therapy

Serpanray

reserpine, 'Panray'

Whole Root Therapy

KOGLUCOID

rauwolfia serpentina, 'Panray'

Supplemental Therapy for NEURO-PSYCHIATRIC CONDITIONS

- Calms hyperactive patients, quiets the noisy, alerts the depressed
- Often precludes electroshock, seclusion and barbiturates
- Tranquilizes and sedates without affecting alertness or responsiveness
- Allows natural sleep
- Clinically proven in anxiety-tension states, compulsive, and other behavioristic disorders
- Non-soporific and well tolerated for prolonged treatment

KOGLUCOID
rauwolfia serpentina, 'Panray'
Supplied in 50 mg. and 100 mg. coated tablets.

Serpanray
reserpine, 'Panray'
Supplied in 0.1 mg., 0.25 mg., 0.5 mg., 1.0 mg., 2.0 mg. and 4.0 mg. compressed, scored tablets. Also available in 2 cc ampules containing 2.5 mg. or 5.0 mg. per cc, for parenteral administration.

Now at a realistic price level, for general hospital use.

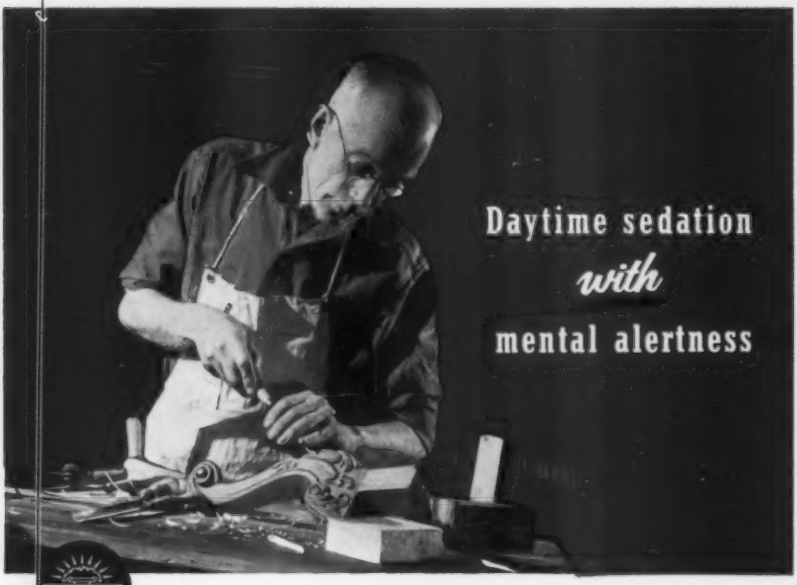
Write for samples, literature

THE Panray CORP. 340 CANAL STREET, NEW YORK 13, N. Y.

Bottles of 100, 500, 1,000 and bulk packing.

Sole Canadian Distributors:
Winley-Morris Co., 6579 Somerled Ave., Montreal 29, P.Q.

© 1955 The Panray Corp., New York, N. Y.



MEBARAL®

BRAND OF MEPHOBARBITAL

—in depressed and agitated states

psychoneurosis
hypertension
hyperthyroidism
convulsive disorders
difficult menopause
hyperhidrosis

Neurotic depression hiding beneath the disguise of multiple physical complaints is an everyday problem in medical practice.

For effective sedation in these cases, and as a means of restoring harmonious relations between patient and environment, Mebaral has been found especially suitable because it lacks excessive hypnotic action.

DOSAGE:

Adults—32 mg. to 0.1 Gm. (optimal 50 mg.), 3 or 4 times daily.

Children—16 to 32 mg., 3 or 4 times daily.

SUPPLIED:

Tablets of 32 mg. (½ grain)
50 mg. (¾ grain)
0.1 Gm. (1½ grains)
0.2 Gm. (3 grains) scored

Mebaral, trademark reg. U. S. & Canada

WINTHROP-STEARNS INC.